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WOMEN'S HEALTH: RAISING AWARENESS OF CERVICAL CANCER

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HEALTH AND ENVIRONMENT

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WOMEN'S HEALTH: RAISING AWARENESS OF CERVICAL CANCER

TUESDAY, MARCH 16, 1999

House of Representatives,
Committee on Commerce,
Subcommittee on Health and Environment,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:57 p.m., in room 2123, Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Stearns, Greenwood, Bilbray, Ganske, Coburn, Lazio, Bryant, Brown, Green, Barrett, Capps, Towns, and Eshoo.

Staff present: Lori Wall, majority counsel; Marc Wheat, majority counsel; Mike Flood, legislative clerk; John Ford, minority counsel, and Kristi Guillory, minority legislative fellow.

Mr. Bilirakis. The hearing will come to order.

Today the subcommittee will hold the first in a series of hearings on women's health concerns by focusing on the issue of cervical cancer, its causes, and its treatments. Each year approximately 15,000 women are diagnosed with cervical cancer in the United States, and almost 5,000 die annually from the disease. Troubling evidence also shows a higher incidence of cervical cancer among minority and disadvantaged populations. The tragedy of these statistics is compounded by the fact that cervical cancer is readily treatable if caught at an early stage.

Last year I sponsored legislation which was enacted into law to reauthorize the National Breast and Cervical Cancer Early Detection Program at the Centers for Disease Control and Prevention. This women's health initiative had strong bipartisan support, including the subcommittee's ranking member, Mr. Brown, the full committee chairman, Tom Bliley, and the full committee ranking member John Dingell.

Today we will learn about recent progress in the fight against this terrible disease. We know that the primary risk factor and leading cause of cervical cancer is the human papillomavirus or HPV, a sexually transmitted disease. Experts estimate that 24 million Americans are infected with HPV, and the incidence of this virus may be increasing.

The good news is that the human immune system can normally clear the virus within 18 months. As a result, many women do not realize they have contracted HPV and they never suffer any health consequences from it. Unfortunately, that is not always the case. It is critical that all women understand the threat of cervical cancer and the importance of regular Pap smear exams. We must increase awareness of how it is transmitted and the importance of early detection. We must also improve methods of detecting the presence of pre-cancerous lesions that develop into cervical cancer.

Later this year I will be participating in a women's health fair in my congressional district. I encourage my colleagues to help educate the public about this disease and other women's health concerns. In that regard, I want to commend the efforts of Senator Connie Mack of my home State of Florida, and Representatives Juanita Millender-McDonald, Rick Lazio, and Tom Coburn in sponsoring a resolution to raise awareness of cervical cancer.

Let me also thank our witnesses for taking the time to join us today, and again extend a special welcome to my Florida colleague, Senator Connie Mack. Connie, do you have the time to wait for the opening statements before testifying?

Senator MACK. Sure.

Mr. BILIRAKIS. Okay. I first want to applaud the work that you and Priscilla have done in the fight against cancer. You certainly will be missed in the Senate, but I trust your leadership in these issues will continue.

I now recognize the ranking member, Mr. Brown of Ohio.

Mr. BROWN. Thank you, Mr. Chairman, for arranging this hearing. I would also like to thank Senator Mack and Congresswoman Eshoo for their fine work, and our other distinguished panelists today. While I am pleased that the subcommittee will hear from a wide range of witnesses, I am disappointed that it was not possible to include a representative from the College of American Pathologists. This organization, representing some 16,000 physicians, offers a unique perspective on the detection, diagnosis, and treatment of cervical cancer. Their input would have been extremely valuable.

The tragedy of cervical cancer is twofold. It is tragic that hundreds of thousands of women confront this disease, a profoundly debilitating and deadly illness. It is tragic that cervical cancer remains such a virulent killer, when it is within our power to prevent it. Cervical cancer is a national and international public health issue. It accounts for 6 percent of cancers diagnosed in women in the United States, taking nearly 5,000 lives. Worldwide, more than 470,000 new cases are diagnosed each year.

In both industrialized and non-industrialized nations, cervical cancer takes its greatest toll on those individuals least able to fight back, minority populations and the economic disadvantaged. Cervical cancer deaths can be virtually eliminated through behavioral changes, early detection, and timely access to treatment, all of which hinge on public awareness. Public awareness fuels change. It can generate the individual and collective actions necessary to achieve a meaningful reduction in cervical cancer rates.

The public needs to know that safe behaviors and proper screening can reduce cervical cancer death rates dramatically. We need to get them the facts about screening test accuracy, new detection methods, and treatment breakthroughs, so they can play an active role in prevention and treatment decisions. We need to emphasize the potential inherent in a national commitment to combat this disease.

The public needs to know about initiatives like the CDC's Breast and Cervical Cancer Early Detection Program, which has reached millions of uninsured women with free screening tests. Public awareness can help us gather the resources needed for CDC and its State and local partners to do more than scratch the surface of this problem. As currently funded, the CDC program reaches only 15 percent of uninsured women. We can do much better than that.

We need to spread the word about initiatives like H.R. 1070, legislation introduced by Ms. Eshoo, which would ensure proper treatment for women who are screened under the CDC program and diagnosed with cancer. Diagnosis is a cruel and fiscally irresponsible exercise when women diagnosed with cancer have no access to treatment, as happens all too often in this society.

Finally, we must all become more sensitive to potential barriers blocking proper cervical cancer screening. Pap smears have dramatically reduced cervical cancer deaths, and it is critical that we do everything in our power to ensure their continued availability.

In that context, we must be vigilant in evaluating the adequacy of Federal reimbursement for Pap smears. Medicare and Medicaid reimbursement directly affects access for two populations particularly vulnerable to cervical cancer: low-income individuals and the elderly. Since private reimbursement is often based on Federal payment rates, our actions indirectly affect millions of women with employer-sponsored or individual insurance coverage. It is imperative that Federal reimbursement accurately reflect the true costs of performing and evaluating Pap smears.

Inadequate data on cervical cancer incidence rates is one of our greatest obstacles, a problem to which too little attention is paid. Our current data lumps different subpopulations together, potentially masking wide variations in cervical cancer rates. It is critical to understand these differences in order to target prevention and treatment initiatives appropriately. Knowledge fuels advocacy, and in the case of cervical cancer, advocacy will save countless lives. That is why today's hearing on cervical cancer awareness is so valuable.

Mr. BILIRAKIS. I thank the gentleman. The Chair recognizes the gentleman from Oklahoma, Dr. Coburn.

Mr. COBURN. Thank you Mr. Chairman. I, too, want to congratulate you on having this hearing. This is a subject matter which, unfortunately, I know way too much about. Last year I treated over 200 women with carcinoma in situ of the cervix. Seven of those had invasive carcinoma. But there were thousands that went through our clinic that had cervical dysplasia.

Not only is the knowledge not out there, the government entities, in terms of this disease, have done a miserable job, in my estimation, of raising public awareness of this. We are not just talking about cervical cancer. There are studies now that show that the human papillomavirus can be transmitted from the mother in utero to her child; that, in fact, you can culture newborn children about 40 percent of the time with this virus. It is theoretically possible that a young woman never exposed could die of carcinoma of the cervix because she contracted that virus in utero or at birth.

There are many studies that are ongoing now to look at these issues. My fear and my worry is not that we will make awareness of these issues possible, but that we will somehow average and marginalize the best public health policy for preventing this disease.

I look forward to the testimony that we have and I yield back my time.

Mr. BILIRAKIS. I thank the gentleman. The gentlelady from California, Ms. Capps.

Mrs. CAPPS. Thank you Mr. Chairman. I appreciate that you are holding this hearing today on such an important topic, raising awareness of cervical cancer, and I want to welcome all of the witnesses.

Senator Mack, I know that you are representing Priscilla as well.

My colleague, Anna Eshoo, a leader in this area, I look forward to hearing from you.

I want to particularly welcome one of our expert panelists today, Dr. J. Thomas Cox, who is a constituent of mine from the University of California at Santa Barbara. An accomplished OB-GYN, Dr. Cox oversees student health services at UCSB, where he runs a program that screens thousands of women for cervical cancer each year. He is an expert in the area of cervical cancer treating, and will today share his broad knowledge on the problems associated with present cervical cancer screening and opportunities to improve this system. I am so proud that Dr. Cox is here to represent the medical expertise worldwide and at UCSB in the 22nd district of California.

As a nurse, I have seen firsthand how important it is to raise awareness of cervical cancer, especially since it is so highly treatable if caught early. The vast majority of cases of cervical cancer are caused by the human papillomavirus, otherwise known as HPV, a sexually transmitted agent that infects the cells of the cervix and slowly causes cellular changes that can result in cancer. Women are often infected with HPV in their teens, 20's or 30's, though the disease can take up to 20 years after the HPV infection starts before the development of the disease begins. It starts with an in situ stage that can be treated, but then as it progresses to an invasive disease, it can often be fatal.

Cervical cancer prevention efforts worldwide have focused on screening women at risk of the disease through Pap smears and treating pre-cancerous lesions. Where screening quality and coverage have been high, these efforts have reduced invasive cervical cancer by as much as 90 percent, and that is a remarkable number. Since pre-cancerous and very early cervical cancers are nearly 100 percent curable, this test can prevent nearly all deaths from cervical cancer.

In reading the remarks that Dr. Cox has prepared for today's presentation, I learned that the decrease in the rate of cervical cancer in the United States is so dramatic that Pap smear screening is one of the few interventions to receive an "A" recommendation from the U.S. Preventive Services Task Force, and that is quite an endorsement. Pap smears have changed the way we approach the problem of cervical cancer, but even with all of our medical advances, there is so much more work to do. Women need more education about cervical cancer and the associated risk factors, including this link with HPV.

Our challenge now is to provide those who have been slow to seek out screening, very often low-income women, with screening opportunities and with access to treatment. And so, just this week, I was honored to join with Congresswoman Anna Eshoo and Congressman Rick Lazio in introducing the Breast and Cervical Cancer Treatment Act. This bipartisan bill gives States the option to provide Medicaid coverage to uninsured or underinsured women who have been diagnosed through the National Breast and Cervical Cancer Early Detection Program, a screening program for low-income, uninsured, or underinsured women. Women who are screened through this program often cannot afford treatment. All of the screening in the world won't help if women who are diagnosed with the disease do not have access to quality treatment for their condition.

So I look forward to learning more from our experts today as we seek to raise the awareness of cervical cancer, its causes, and its treatments. And I hope that we can all work together to enact the Breast and Cervical Cancer Treatment Act as quickly as possible.

I yield back the balance of my time.

Mr. BILIRAKIS. I thank the gentlelady. Does the gentleman from Florida, Mr. Stearns, have a quick opening statement?

Mr. STEARNS. A quick opening statement.

Mr. BILIRAKIS. You are recognized.

Mr. STEARNS. Thank you, Mr. Chairman. I appreciate you holding this important hearing, and, of course, I look forward to hearing from our distinguished Senator, who is retiring. I appreciate the opportunity to see him again.

The average age at diagnosis is 45, but can occur in women 20 to 30 years old. We are not sure what causes cervical cancer, but we do know that there are a number of pre-disposing factors. These include multiple sex partners, early sexual activity, and early child bearing. But the good news is that routine Pap smears are very effective in detecting abnormal cells, and if detected in time, can be treated with promising results.

I look forward to the hearing, Mr. Chairman, and I appreciate Senator Mack being here.

[The prepared statement of Hon. Cliff Stearns follows:]

PREPARED STATEMENT OF HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Thank you, Chairman Bilirakis, for holding this very important hearing that deals with a very serious women's health issue.

I look forward to hearing from our distinguished panel of witnesses. In particular, I look forward to hearing from my own Senator, Connie Mack.

When we think about the various cancers that can afflict women, we rarely focus on cervical cancer. Yet, 2-3 percent of all women over the age of 40 will develop some form of cervical cancer. That translates to about 5,000 deaths per year.

The average age at diagnosis is 45, but can occur in women 20-30 years old. We are not sure what causes cervical cancer, but we do know that there are a number of predisposing factors. These include: multiple sex partners, early sexual activity, or early childbearing (less than 16 years of age).

Another factor that must be mentioned is that women who were exposed to the drug DES (diethylstilbestrol) might be at greater risk of developing certain types of cervical cancer due to this exposure.

The good news is that routine pap smears are very effective in detecting abnormal cells and if detected in time can be treated with promising results. Because there are no discernible symptoms in the early stages, it is vital that women see their physician on an annual basis since early intervention with proper treatment can save 80% of women. Once this disease progresses and spreads to other organs the survival rate drops significantly.

I look forward to hearing from our witnesses and believe that through hearings such as this we can educate the public about this disease and the need for medical check ups on a regular basis.

Mr. BILIRAKIS. I thank the gentleman. Unless it is imperative that the latecomers make an opening statement, I would like to go ahead. Greg, do you have a quick opening statement?

Mr. GANSKE. In deference to the chairman, I will submit my opening statement.

Mr. BILIRAKIS. I appreciate that.

Well, let's go into the first panel then. Joining Senator Connie Mack in the first panel is a lady who I always refer to as to the conscience of this subcommittee. She is a very effective Congresswoman with a fantastic heart. Anna, you are recognized.

STATEMENTS OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA; AND HON. CONNIE MACK, A UNITED STATES SENATOR FROM THE STATE OF FLORIDA

Ms. ESHOO. Thank you very much, Mr. Chairman. Is this on? Now it is. We are more accustomed to the microphones at the other side of the table here.

Mr. Chairman and members of the committee, our distinguished ranking member, it is a special privilege for me to give testimony today to the subcommittee that I am a member of, and how proud I am to be a member of the committee. This is an all important issue, and I think that the entire Nation should be grateful today that this hearing is taking place.

I am especially proud to be seated next to Senator Mack, and I want to salute him for his outstanding service in the Congress of the United States. Everyone will miss your leadership and your service here. I want to express my gratitude to him and to California Representative Juanita Millender-McDonald for their leadership on the cervical cancer public awareness resolution.

Resolutions are important because I think they set the foundation on which legislation can follow, and so I am very pleased to be a part of that resolution because it raises public awareness. And we know that we can make a difference when we set our minds to it, to raise the awareness of people in the country, and in this case about cervical cancer, with special regards to its risks, certainly the prevention, and most importantly, treatment.

Why? Because 70 percent of women in a recent study in our country did not even know what causes cervical cancer. Less than a quarter of them had ever even heard of HPV, which is the leading cause of this disease. Cervical cancer is a killer. I should say that again. Cervical cancer is a killer. Of the 15,000 women who are diagnosed with cervical cancer each year, 5,000 will die. That is a huge, huge number of human beings. And we know that we can do something about this. That is a mortality rate of over 30 percent. In this enlightened Nation, we know we can do better. In fact, we must.

But even more tragic is the fact that this disease is actually preventable. Since the introduction of the Pap smear, as Congressman Lois Capps just stated, since 45 years ago, cervical cancer in our country has dropped 75 percent. According to the National Cancer Institute, the 5-year survival rate is 91 percent when cervical cancer is detected and treated at an early stage.

In 1990, Congress took a very important step. I wasn't here then, but to those of you that were, I salute you, because you took a very important step in the fight against this deadly disease by passing the Breast and Cervical Cancer Mortality Prevention Act. The law authorized a cervical cancer screening program for low-income, uninsured, or underinsured women through the CDC. It was a very important first step, but it was only a first step. Because while the current program covers screening services, it does not cover treatment for women who are found to be positive through the program.

Representative Rick Lazio, Congresswoman Capps, and myself introduced last week a bill that would address this. The bill, H.R. 1070, would establish an optional State Medicaid benefit for the coverage of certain women who are screened and diagnosed through the CDC program. I don't really think, Mr. Chairman, that the Federal Government should be saying to women, "We are willing to help you be screened and then you are left to your own devices when it comes to treatment." So this is what the bill seeks to close the gap on.

I set a goal with Representative Lazio when we introduced this last week—and we missed you, Lois, there, and we understand why you couldn't be—that by Mother's Day we would have 218 co-sponsors on a bipartisan basis in the House. And I hope, Mr. Chairman, that you will have a hearing on the bill. I think that this is something that we can, indeed, get done for the American people.

So, this providing breast and cervical cancer treatment to women who cannot afford it otherwise, we believe should be a Federal priority. We know that there is not Republican cancer or Democratic cancer. When we go home to our constituents, we should have an united voice and a united front on this.

So, we will look forward to taking the next step, not only on the resolution, but on the bill, and I want to thank you, Mr. Chairman, for your leadership always, and our distinguished ranking member, Sherrod Brown. I think it is the real privilege of my congressional career to be part of this committee, because we can really make a difference in people's lives. So thank you for giving me this opportunity.

[The prepared statement of Hon. Anna G. Eshoo follows:]

PREPARED STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Thank you Mr. Chairman. As a *member* of this distinguished committee, I am extremely proud that we are tackling the issue of cervical cancer. As a *witness* for the hearing, I am grateful for the opportunity to contribute my insight into how we, in Congress, might help to fight this battle.

I also want to express my gratitude to my colleague from California, Rep. Juanita Millender-McDonald, and Senator Connie Mack for their leadership on the Cervical Cancer Public Awareness Resolution.

This resolution seeks to raise public awareness of cervical cancer among women, specifically with regard to risks, prevention and treatment.

- For instance, 70% of women in a recent survey did not know what causes cervical cancer and less than a quarter had even heard of the human papilloma virus (HPV), which is the leading cause of the disease.

I am an original cosponsor of the Millender/Mack resolution because I know that knowledge saves lives.

Cervical cancer is a killer.

- Of the 15,000 women who are diagnosed with cervical cancer each year, 5,000 will die. That is a mortality rate of over 30%.

But even more tragic is the fact that this disease is preventable.

- Since the introduction of the Pap smear test 45 years ago, cervical cancer in the U.S. has dropped 75%.
- According to the National Cancer Institute, the five-year survival rate is 91% when cervical cancer is detected and treated at an early stage.

In 1990, Congress took the first step in the fight against this deadly disease by passing the Breast and Cervical Cancer Mortality Prevention Act.

- This law authorized a cervical cancer screening program for low-income, uninsured or uninsured women through the Centers for Disease Control (CDC).

But this was only the first step. While the current program covers screening services, it does not cover treatment for women who are found to be positive through the program.

A bill Rep. Rick Lazio and I introduced last week would fill that gap.

Our bill, the Breast and Cervical Cancer Treatment Act (H.R. 1070) would establish an optional state Medicaid benefit for the coverage of certain women who were screened and diagnosed through the CDC program.

Our bill would replace the current system of providing treatment through an ad hoc patchwork of providers, volunteers, and local programs scrambling to find treatment dollars with a consistent, reliable source of health care coverage.

Mr. Chairman, we have the technology to fight cervical cancer. But we must pair this with the will to help women fight the battle. Because women with life threatening diseases should be concentrating their energies on treatment, not payment.

Mr. Chairman, the federal government should not be in the business of telling women, “We’ve helped you find out you have cancer, now you’re on your own.”

With over 80 bipartisan cosponsors of the bill already, Congress has sent a message that this bill—the Lazio/Eshoo Breast and Cervical Cancer Treatment Act—should be a federal priority.

Providing breast and cervical cancer treatment to women who can not otherwise afford it, should be a federal priority.

So I ask you today, Mr. Chairman, to not allow this to be the only hearing this subcommittee holds on cervical cancer. Hold a hearing on H.R. 1070 and take the next step toward helping women fight cervical cancer.

Thank you Mr. Chairman for this opportunity to testify before my own distinguished subcommittee on this very important issue. I look forward to hearing from the other witnesses.

Mr. BILIRAKIS. Thank you very much.

Ms. ESHOO. I see the red light and I’ll shut my microphone off.

Mr. BILIRAKIS. Thank you very much. Knowing you, Anna, and having worked with you these many years, I expect you’ll probably have 218 co-sponsors by your timeline.

It is a great privilege to yield now to Senator Mack.

STATEMENT OF HON. CONNIE MACK

Senator MACK. Well, Mr. Chairman, let me add my voice to others in expressing not only my gratitude for the opportunity to speak before this committee, but also to thank you for highlighting this particular issue. Some of you probably remember that I was diagnosed with melanoma back in 1989, right after I was elected to the Senate. I don’t have to worry about that today, because it was detected early. That early detection probably took place because of the death of my younger brother Michael, who died of the same cancer. It made me so aware of it that I was, as I have said before, Priscilla and I check each other like two baboons looking for—you get the message. I am alive today because of early detection.

Many of you know that my wife Priscilla was diagnosed with breast cancer a number of years ago, and she is a survivor today because she detected the breast cancer early. Most of you don’t know, in fact, probably all of you don't know, that our daughter Debbie was diagnosed with cervical cancer back in 1990. She is a survivor today because of early detection. She was aware of the cancers in our family, and as families become sensitive to that, they are aware of the types of actions they ought to be taking on their own to protect themselves.

So, I commend you for holding this hearing because, I will tell you, just as a result of doing the hearing, someone is going to hear that message. Priscilla and I have already experienced it, and I suppose that you have as well; that people will come up to you and say, "Because I heard such and such, I did such and such, and as a result today, I am cancer-free."

So, I not only commend the chairman, but all of you who have shown such an interest in this disease. I commend all of you.

According to the American Cancer Society, nearly 1,000 women in Florida will be diagnosed with cervical cancer in 1999. This year Florida will have the third largest number of new cases of cervical cancer.

Yet, despite significant progress being made in the war on cancer, not all segments of the U.S. population have benefited to the fullest extent from the advances made in the understanding of cancer. According to the U.S. Institute of Medicine report, "The Unequal Burden of Cancer," rates of cervical cancer are significantly higher in Hispanic and African-American women. We simply must do better. We must reinforce our effort to eradicate the terrible disease, but we also must continue and expand our efforts to see that this information and the knowledge and the education gets to all women in America.

Research, education, and early detection are the most effective weapons that we have in the war on cervical cancer. In an effort to help increase awareness and education about this disease, today I will introduce a Senate resolution to designate the month of January as National Cervical Health Month. I am pleased that Senator Diane Feinstein and 31 other members of the Senate have agreed to be original co-sponsors of this Senate resolution. I know from what has been said already here this afternoon that Juanita Millender-McDonald and many of you have agreed to co-sponsor similar legislation in the House of Representatives.

Research is the key to finding a cure for cervical cancer, and significant progress is being made in this regard. Just last month, for example, the National Cancer Institute took the rarely used step of issuing a clinical announcement urging that physicians should give strong consideration to adding chemotherapy to radiation therapy in the treatment of invasive cervical cancer. According to NCI Director Rick Klausner, this will likely change the standard of treatment for cervical cancer. Dr. Mitchell Morris of the M.D. Anderson Cancer Center called this new treatment approach "the first fundamental advance in the treatment of cervical cancer in more than 40 years."

Mr. Chairman, I am proud to say that in our home State of Florida, there are several studies that are underway. Scientists at the University of Miami Sylvester Cancer Center are studying a new type of cervical cancer immunotherapy. Let me just stop there for a moment.

I guess it was just fate that 1 day, wandering through a bookstore, I saw a book called Transform Cell, and because it was about melanoma. it caught my attention. I bought the book and read through it, and as you made your way through it, you found there were a couple of terms that we really weren't hearing. Most of us are familiar with the modalities of chemotherapy, radiation therapy, and surgery as the means of addressing cancer. But there were a couple of new words that were coming into discussion; that was immunotherapy. Dr. Rosenberg really believes that we could turn on the immune system to fight cancer—and that for some reason, the immune system saw cancer cells as just a normal cell in the body. And so he began an active pursuit, primarily in the area of melanoma in kidney cancers. The concept now is spreading out into many other areas.

In addition to immunotherapy, we are hearing people talk about now gene therapy—again, ideas that just 10 or 12 years ago didn't really seem to even be on the horizon. And I think that the Congresses in the past have done a tremendous job in providing the resources to provide the money for the basic research that creates the knowledge that then becomes the magnet for investment to develop new drugs and new treatment.

Again, at the Sylvester Cancer Center, they are developing killer cells specifically designed to target cancer cells which express human papillomavirus. By eradicating these cells, the hope is to kill the tumor, even if the cancer has spread.

At the H. Lee Moffitt Comprehensive Cancer Center in Tampa, studies are underway to develop a cervical cancer vaccine using some of the same characteristic of the human papillomavirus. They are also examining biomarkers to develop cervical cancer before malignant changes occur.

And just in my last comment, and I do take off my Senate hat, I take off my political hat, I take off a Republican hat, I put them aside and I just speak to you all for a moment from the perspective of a father thinking of my daughter Debbie, of a husband thinking of my wife Priscilla. I say that I am stunned, frankly, by the President's budget proposal. Last year the administration made a major commitment to the fight against cancer with a commitment of a 55 percent increase over time. If my memory holds right, I think the President's budget calls for a 2, maybe 2.6 percent increase in NIH. I would ask all of us, again setting aside those labels that I used a minute ago, let's rally around. We made a commitment a couple of years ago for the effort of doubling the investment that we make at NIH, which is obviously more than cancer. It is Parkinson's disease; it is sickle cell anemia; you name the disease and we are pursuing it. I think this is the greatest investment that we can make. So I just would appeal to all of you, let's re-commitment ourselves to this commitment we made less than 2 years ago to double the investment at NIH.

And I thank you again, Mr. Chairman, for the opportunity.

[The prepared statement of Hon. Connie Mack follows:]

PREPARED STATEMENT OF HON. CONNIE MACK, A U.S. SENATOR FROM THE STATE OF FLORIDA

Mr. Chairman, I want to commend you for holding this important hearing, and I thank you for inviting me to testify this afternoon.

The issue of cervical cancer is one which is deeply personal to my wife, Priscilla, and to me. In 1990, our daughter, Debbie, was diagnosed with cervical cancer. Because of our family history with cancer, Debbie was aware that she had an increased risk of cancer and she made sure to take advantage of early detection screening procedures. Fortunately, her cervical cancer was detected at an early stage, and she was treated successfully with surgery. Not long after her treatment, she gave birth to our third grandson. Debbie's experience with cervical cancer exemplifies the fact that early detection saves lives.

According to the American Cancer Society, nearly 1000 women in Florida will be diagnosed with cervical cancer in 1999. This year, Florida will have the third largest number of new cases of cervical cancer. Yet, despite significant progress being made in the war on cancer, not all segments of the U.S. population have benefitted to the fullest extent from the advances made in the understanding of cancer. According to the U.S. Institute of Medicine report, "The Unequal Burden of Cancer," rates of cervical cancer are significantly higher in Hispanic and African-American women. We simply must reinforce our efforts to eradicate this terrible disease.

Research, education, and early detection are the most effective weapons we have in the war on cervical cancer.

In an effort to help increase awareness and education about this disease, today I will introduce a Senate Resolution to designate the month of January as "National Cervical Health Month." I am pleased that Senator Dianne Feinstein and 31 bipartisan colleagues in the Senate have agreed to be original co-sponsors of this Senate Resolution. I understand that Rep. Juanita Millender-McDonald will be introducing similar legislation in the United House of Representatives.

Research is the key to finding a cure for cervical cancer, and significant progress is being made in this regard. Just last month, for example, the National Cancer Institute took the rarely-used step of issuing a Clinical Announcement urging physicians to give strong consideration to adding chemotherapy to radiation therapy in the treatment of invasive cervical cancer. According to NCI Director Rick Klausner, this will likely change the standard of treatment for cervical cancer. Dr. Mitchell Morris of the M.D. Anderson Cancer Center called this new treatment approach, "the first fundamental advance in the treatment of cervical cancer in more than 40 years."

I'm also proud to say that several cutting-edge cervical cancer studies are taking place in my home state of Florida. Scientists at the University of Miami Sylvester Cancer Center are studying a new type of cervical cancer immunotherapy. They are developing "killer cells" specifically designed to target cancer cells which express human papilloma (HPV). By eradicating these cells, the hope is to kill the tumor, even if the cancer has spread. At the H. Lee Moffitt Comprehensive Cancer Center in Tampa, studies are underway to develop a cervical cancer vaccine using some of the same characteristics of the human papilloma virus. They are also examining biomarkers to detect cervical cancer before malignant changes occur.

The U.S. Senate and House, working in bipartisan cooperation, have embarked upon an historic mission to double funding for the National Institutes of Health over the next five years. Last year, the Congress overwhelmingly passed, with bipartisan support, a $2 billion increase for the National Institutes of Health—the largest increase in NIH history.

With the tremendous progress being made in cervical cancer and other diseases, I was astonished and extremely disappointed the President's FY 2000 budget only calls for a meager 2.6% increase for medical research at the NIH. This is simply unacceptable. The President's proposed budget means a cease-fire in the war against cancer, Parkinson's disease, Alzheimer's disease and other illnesses. In effect, the President's proposal is a formal act of retreat in the heat of battle.

I was also shocked that the President's FY 2000 budget calls for not one additional penny of funding for the Breast and Cervical Cancer Screening program at the U.S. Centers for Disease Control & Prevention. For FY 1999, the bipartisan Congress provided a $16 million increase. By contrast, the President's request for FY 1999 was for an increase of less than $1 million for this life-saving program, and he proposes no increase for next year.

When it comes to cervical cancer research and screening, the President just doesn't get it. It's obvious the leadership on these initiatives will have to come from this end of Pennsylvania Avenue. It will be through the bipartisan commitment of the Senate and House that these important research and detection programs will receive adequate funding. I am here to pledge my support, and to work with my colleagues in Congress to make sure this happens. Far too many lives depend upon it.

Again, Mr. Chairman, thank you for holding this important hearing and for allowing me the opportunity to appear before this committee.

Mr. BILIRAKIS. And I thank you, Connie.

Yes, I would wager that most of the members of this subcommittee have basically signed on the pledge of doubling NIH funding, and that is certainly one of our great big causes, working with John Porter and Bill young on the Appropriations Committee.

Connie, I really have no questions of you and Anna. I just want to endorse all of the great things that were said about you yesterday in Tallahassee, where we were together for that legislative summit. Hopefully, you will continue to use your high profile for this important cause.

Senator MACK. Well, thank you for the encouragement.

Mr. BILIRAKIS. I commend you both for testifying on this important issue.

At this point, I would ask unanimous consent that the opening statements of all members of this subcommittee and the testimony of Congresswoman Juanita Millender-McDonald be made a part of the record. Without objection that will be the case.

[The prepared statement of Hon. Juanita Millender-McDonald follows:]

PREPARED STATEMENT OF HON. JUANITA MILLENDER-MCDONALD, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. Chairman, I would like to thank you, Chairman Bliley, Ranking Member Dingell, and Ranking Member Brown for supporting my efforts to raise awareness of cervical cancer by serving as original cosponsors of the Cervical Cancer Awareness Resolution. I would also like to thank all of the Subcommittee members who served as original cosponsors of this resolution, and in particular, Congressmen Rick Lazio and Tom Coburn, who have been tireless advocates in our effort to introduce and pass this resolution to help educate women on this fatal, yet in most cases, preventable disease.

In 1990, Congress passed the Breast and Cervical Cancer Mortality Prevention Act, which enabled the CDC to establish the National Breast and Cervical Cancer Early Detection Program. This Program offers community-based screening services for women with little access to health care, education programs on the benefits of early screenings, quality assurance standards for cancer testing, and surveillance system on the effectiveness of these programs.

I applaud the efforts of our colleagues on the Committee who are working to strengthen these programs and create greater access to screening and treatment for medically underserved communities. It is this lack of access and poor understanding of cervical cancer that illuminate the challenge before us today.

More than 50 years ago, Dr. George N. Papanicolaou developed what is considered the most effective cancer screen in the history of medicine, the Papanicolaou test or what we call the Pap smear test. Although it is not perfect and we welcome technological advances in the field of medicine, it is a remarkable tool in saving lives and preventing invasive cervical cancer. The real problem is making sure women understand what cervical cancer is, what steps they can take to reduce the likelihood of getting cervical cancer, how it can be detected early and what all of their treatment options are when facing this disease.

As you know, tomorrow Committee Members Lazio and Coburn, and I will introduce the Cervical Cancer Public Awareness Resolution because we want to tackle this problem of misinformation, confusion and discomfort that too many women continue to feel on this issue. Our resolution is part of a national campaign to raise awareness on cervical cancer among women and encourage Americans to become more educated on related risk factors, prevention and treatment.

An estimated 15,000 women in the United States develop cervical cancer each year according to the American Cancer Society. The World Health Organization and the National Institutes of Health state that the principal cause of cervical cancer is the human papillomavirus or HPV infection, which is one of the most common sexually transmitted diseases (STDs). Fortunately, when cervical cancer is detected at an early stage, the five-year survival rate is 91 percent, according to the National Cancer Institute. The Centers for Disease Control and Prevention report that the mortality rate among American women with cervical cancer declined from 1960 to

1997 in large part due to the extensive use of the Pap smear test. However, in 1997 the number began to rise I fear because the message on cervical health has not reached enough women.

In October 1997, a Gallup survey commissioned by the College of American Pathologists found that although 87 percent of the women surveyed know they should have a Pap test every year, nearly 40 percent of these same women failed to do so in the previous year. One in four of the women who had not had an annual Pap test said they "didn't have the time." The reasons include the belief that they are too old, feeling embarrassed or afraid of tie results, or thinking it is too expensive. While all of these reasons are valid, they are not acceptable when one considers that 80 percent of the women who die of cervical cancer have not had a Pap test in five years or more.

As with other health issues, there is a tremendous chasm between minority, lower-income and/or less educated women as opposed to financially stable, employed and/or well educated women. According to the Department of Health and Human Services (HHS), one out of every three Hispanic women reported that they failed to get a Pap test in the preceding three years, compared with about one-quarter of all American women. In addition, another survey by HHS on Working Women's Health found that 87 percent of employed women had a recent Pap test within the past 3 years while 73 percent of women not in the labor force had done so. Pap testing for women in managed care plans living in certain regions of the country is also lower, according to the 1998 State of Managed Care Quality report. For example, 69 percent of women living in the mid-western Mountain states had cervical cancer screening while 76.5 percent of the women in New England states had cervical cancer screening.

More women of color are dying from this disease as well. For instance, the rate of mortality for African American women is nearly twice that of Caucasian women according to HHS. Equally disturbing is the high rate of STD transmission within this community since HPV is the most common STD. In my own district of South-Central Los Angeles, the County Health Department reports that the rates of STDs among African Americans are up to 20 times higher than among whites and STD morbidity (except Chlamydia) is concentrated disproportionately in Central and South-Central LA. HPV infection and cervical cancer are serious risks for the inner-city communities I represent.

That is not to say that HPV infection is the only cause of cervical cancer, but rather, an important part of this health problem that is far too often misunderstood by women. According to the National Cancer Institute, other risk factors include smoking although it is not clear exactly how or why. Women whose mothers were given the drug diethylstilbestrol (DES) during pregnancy to prevent miscarriage from approximately 1940 to 1970 are at increased risk as well. There is also evidence indicating that women whose immune systems are weakened as a result of an organ transplant where drugs are administered to prevent rejection of the new organs are at higher risk.

Although the risk factors for cervical cancer can vary, the cultural, financial and even geographical barriers that complicate the fluid delivery of quality health care linger as a dangerous indication of the need for open and honest dialogue on this issue. As Members of Congress already in the public eye of our communities, we should do our part in raising public awareness on this critical issue.

Mr. Chairman, I applaud your work today and appreciate your giving me the opportunity to work with you in meeting this goal. Once again, I thank you for your support of the Cervical Cancer Public Awareness Resolution and I look forward to working with you to advance this cause.

[Additional statements submitted for the record follow:]

PREPARED STATEMENT OF HON. RICK LAZIO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Mr. Chairman, one of my priorities as a Congressman is to fight cancer by bringing attention to this dreaded disease. We must find solutions for the women and men in our country who suffer from all forms of cancer.

I founded the House Cancer Awareness Working Group, a bipartisan working group which provides an educational forum where cancer patients, advocates, and scientists can heighten public and congressional awareness and offer recommendations to address the most pressing issues in the battle against cancer. We have focused on issues such as determining the best age for mammography screening, detecting prostate and ovarian cancer, preventing the onset of cancer through healthy eating, the cancer disparities between races and ethnic groups, the progress of genetic research, and the need for anti-discrimination legislation. Gaining the recognition of more than 40 Members of Congress, as well as the American Cancer Society and the National Cancer Institute, the Group will continue to fight cancer here in Congress.

In addition to the Working Group, I have recently re-introduced my legislation, The Breast and Cervical Cancer Treatment Act of 1999. This legislation will complete the CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) by adding a treatment component to the extremely successful screening program for low-income women who have little or no health insurance. We encourage early detection and screening, but treatment must be coupled with screening if we are ever going to save lives.

My legislation, introduced with Ms. Eshoo, would create an optional state program to allow these women to be covered under Medicaid while they are being treated for cancer. The hallmark of fairness is to ensure that women stricken with cancer can have the hope of a cure. This legislation is the right thing to do and I hope that every member of this committee will support it through cosponsorship.

Also, I have recently partnered with Rep. Millender-McDonald and Rep. Coburn in introducing a cervical cancer resolution recognizing the severity of the issue of cervical health and its relation to cancer as well as encouraging public awareness, education, and early detection.

Mr. Chairman, thank you for having this hearing. I look forward to working with you in taking the appropriate steps to combat this dreaded disease in every way we know how!

PREPARED STATEMENT OF HON. TOM BLILEY, CHAIRMAN, COMMITTEE ON COMMERCE

Mr. Chairman, I applaud you for holding this hearing today on the issue of cervical cancer. I am proud to say this Committee is the first committee to hold such a hearing on this issue. I have worked very hard over the years to pass legislation of importance to public health and especially those related to the special health concerns of women. For example, I recently sent a letter to Dr. Richard Klausner, Director of the National Cancer Institute (NCI), on the importance of health issues, specifically in regards to women's health. One issue that I addressed was cervical cancer.

In the response to my letter, NCI stated there are 5,000 women who die from cervical cancer each year. In addition, thousands of others are diagnosed with the disease and begin treatment. In light of these alarming numbers, it is somewhat surprising the lack of attention given to cervical cancer in comparison to other diseases. A recent study by Wirthlin Worldwide indicated 70% of the women they surveyed did not even know what causes cervical cancer. Today, we have the sound medical evidence that demonstrates that human papillomavirus or "H-P-V", while not the only cause of cervical cancer, is the primary cause of cervical cancer. It is important that we have this hearing today to raise the awareness of cervical cancer and provide much needed information on the disease.

There are many new advances being made in cervical cancer detection, prevention and treatment. Today, we will hear about some of the new advances and treatments that are being made in the fight against cervical cancer. Until the day that cervical cancer becomes a disease of the past, we need to do all we can to make sure women know about cervical cancer, its causes and its treatments.

I would like to welcome all of our panels here today to testify. I would especially like to welcome Sen. Connie Mack for being with us today and for all of his efforts in the fight against cancer. In addition, I would like to thank Rep. Anna Eshoo, a member of this subcommittee, for appearing before it today. Thank you all for coming and testifying before us today.

PREPARED STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. Chairman, it is a pleasure to see this Subcommittee return to such an important issue. This is an area of public health where the Subcommittee has been aggressive and successful in enacting important legislation benefitting women's health.

In 1988, Congressman Dingell and I sponsored the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which protects women from substandard Pap smears. In 1990 and 1993, I sponsored laws creating and strengthening the Federal government's programs to screen, prevent and treat breast and cervical cancers—the Breast and Cervical Cancer Mortality Prevention Act of 1990 and the Breast and Cervical Cancer Amendments of 1993.

At the time, we believed that these laws would help reduce cervical cancer's mortality. We funded comprehensive screening programs for low-income women, established quality guidelines for cytological screening, and supported health training and public education.

There are indications that these efforts, in conjunction with improvements in diagnosis and treatment, have borne some fruit. Deaths and the incidence of cervical cancer appear to have marginally declined in this country.

But we must do much more. In 1990, cervical cancer caused 6,000 deaths. Last year, it caused 4,800 deaths—most of them preventable with proper screening and treatment. Despite the availability of such services to low-income women, there is evidence that this is not as widely known as it should be. That is why I strongly support Congresswoman Millender-McDonald and my colleagues on this Subcommittee for sponsoring the cervical cancer awareness resolution.

To save more lives, the next step for the members of this Subcommittee and the Congress will be to determine whether Federal funding and reimbursement for preventive screening and follow-up treatment is adequate.

I join my colleagues in welcoming our witnesses and look forward to their testimony.

PREPARED STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

I want to thank Chairman Bilirakis for scheduling this important hearing so that we can learn more about how to prevent and treat cervical cancer.

Each year in the United States, 15,000 women are diagnosed with and 5,000 women will die from cervical cancer.

In fact, it is the second most common form of cancer effecting women today.

The good news is that we have learned a great deal about what causes cervical cancer.

The bad news is that there is no cure when it is not detected early on.

With this in mind, there are several steps that Congress can and should take to help reverse this trend.

First, we need better education of the health risks and behaviors that can help prevent cervical cancer.

Statistics indicate that while 93% of women with cervical cancer had the sexually transmitted disease HPV, the overwhelming majority of women have never heard of HPV—not to mention how to prevent it.

Second, federal health insurance programs should cover not only the screening to detect and diagnose cervical cancer—but also financial assistance to treat the women who test positive for this disease.

The federal government should lead by example when it comes to providing the most comprehensive health insurance for women.

Finally, we need to continue to increase funding for research by doubling the NIH budget.

Increasing research at NIH will give the thousands of women who are annually diagnosed with cervical cancer the best chance at finding a cure.

I look forward to hearing from our distinguished witnesses. Before Congress can help educate our constituents, we need to be fully aware ourselves.

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

I applaud Mr. Bilirakis for scheduling this hearing on the important issue of cervical cancer. I also would like to applaud the bipartisan efforts of my colleagues in sponsoring H. Con. Res. 5, a resolution to promote public awareness of cervical cancer. This resolution points out the serious problems associated with cervical cancer and calls on the country as a whole to learn more about this disease through public awareness and education.

Last year, H.R. 4683, the Women's Health Research and Prevention Amendments of 1998, did not address certain important issues that affect women's health such as sexually transmitted diseases. Left untreated, sexually transmitted diseases can cause infertility, birth defects, disease, and can ultimately lead to death.

Perhaps now we can begin open, frank discussions of this topic since the primary cause of cervical cancer is one of the most common sexually transmitted diseases, human papillomavirus ("HPV"). Up to 80 percent of women develop HPV at some point in their lives. HPV is unique in that it is largely asymptomatic, can cause cancer, and is so widespread.

Each year, an estimated 15,000 cases of cervical cancer are diagnosed, and 5,000 women die from this disease. Even though the incidents of death are lower when compared to other cancers, the impact of cervical cancer is felt worldwide. It is the leading cause of death among women in developing countries. The sad part about this is that most of these deaths are preventable.

The pap smear is the most effective tool for detecting cervical cancer; however, in many cases the results are inconclusive. Studies indicate that testing for HPV may be a more effective test for cervical cancer than pap smears. Regular pap smears combined with HPV testing would be a woman's best defense against cervical cancer.

I am pleased that my colleagues in the majority on this committee have shown interest in this important issue. We must raise awareness about cervical cancer if we are to stop women from needlessly dying from this curable disease. Let this hearing be a first step in enacting legislation that will ensure that the issue of cervical cancer receives the attention that it deserves. None of us should be satisfied until the cervical cancer death rate drops to zero.

Thank you.

Mr. BILIRAKIS. Call forward the second panel: Dr. Ronald Valdiserri, Deputy Director, Center for Disease Control and Prevention; Dr. Nancy Lee, Associate Director for Science, also with the Center for Disease Control and Prevention; Dr. Douglas Lowey, Deputy Director, National Cancer Institute, and Dr. Edward Trimble, Head Surgery Section, National Cancer Institute.

Welcome to this hearing. I apologize for the late start. Often when we're scheduled for a hearing, votes take place on the House floor, and that is why we were delayed in getting here.

Your written statements are a part of the record, and I would appreciate it if you could stay as close to the 5-minute light as you can in the process of complementing your written statement.

Dr. Valdiserri, we will start off with you.

STATEMENTS OF RONALD O. VALDISERRI, DEPUTY DIRECTOR, CENTER FOR DISEASE CONTROL AND PREVENTION; NANCY C. LEE, ASSOCIATE DIRECTOR FOR SCIENCE, CENTER FOR DISEASE CONTROL AND PREVENTION; EDWARD L. TRIMBLE, HEAD SURGERY SECTION, NATIONAL CANCER INSTITUTE; AND DOUGLAS R. LOWEY, DEPUTY DIRECTOR, NATIONAL CANCER INSTITUTE

Mr. VALDISERRI. Good afternoon, Mr. Chairman and subcommittee members. I am Ron Valdiserri, Deputy Director of the National Center for HIV, STD, and TB Prevention at the Centers for Disease Control and Prevention. I thank you for the opportunity to testify today about what we know about the relationship between human papillomavirus infection and cancer of the uterine cervix.

Human papillomavirus, otherwise known as HPV, is a virus that infects the skin and mucus membranes. New laboratory techniques to identify HPV became available in the 1980's and revolutionized what we know about the epidemiology of HPV infection. Over 80 different types have been identified. Some viral types infect the hands and feet, causing common warts, while others are sexually transmitted and affect the genital area. Of the 30 or so types that infect the genital region, some cause clinically apparent genital warts and also low-grade Pap smear abnormalities, but are not associated with cervical cancer; hence, they are termed low-risk types. Approximately 10 types are considered high risks for cancer, in that they are found in approximately 95 percent of all tissue specimens from cervical cancer patients.

It should be stated, however, the genital HPV infections, while they are not curable, that the vast majority are benign. Definitive studies on prevention strategies, including male and female condoms and newly developed microbicides, are, unfortunately, very limited. Most people who are infected with HPV are asymptomatic and do not develop warts. Infected men and women who develop genital warts are diagnosed by their typical appearance, usually without laboratory verification of the virus. Most women with HPV are diagnosed indirectly by Pap smear or by biopsy findings rather than having the HPV directly detected.

It is estimated that at least 50 percent of sexually active adults will acquire genital HPV infection. As many as 45 million Americans may already be infected, and an estimated 5 million new cases develop each year, making HPV the most common sexually transmissible disease. Again, more than 90 percent of people with HPV infections do not have symptoms, although they are potentially infectious.

Key risk factors for cervical HPV infection in women include a younger age and the number of sex partners. Cigarette smoking and oral contraceptive use have also been cited as risk factors. Unfortunately, risk factors for HPV in men have not been very well studied.

In most sexually active women who acquire HPV infection of the cervix, the virus becomes undetectable over time without specific treatment and causes no problems. However, for women whose infections persist, these women are more likely to be infected with the cancer-associated HPV types. Approximately 5 to 10 percent of women with the high-risk types of HPV infection will develop cervical cancer without Pap smear screening and early treatment. Large studies comparing women with cervical cancer to those without it have shown that infection with one of these high-risk HPV types increases the risk of cervical cancer by at least 30-fold, a level similar to or higher than the risk of lung cancer association with cigarette smoking.

Laboratory and animal experiments also support a causative role for HPV and cervical cancer. In summary, there is now widespread consensus among cancer researchers that high-risk types of genital HPV play a causative role in cervical cancer and probably other types of anogenital cancer, including cancer of the penis and anus. Having HPV seems to be necessary for developing cervical cancer, but just having the infection alone is not sufficient to produce cancer. Other co-factors such as smoking, an abnormal immune system, and other genital track infections may also be important. My CDC colleague, Dr. Nancy Lee, will present an overview of cervical cancer screening programs later during this panel.

The recognition that cervical cancer is caused by a highly prevalent STD has important implications for public health. Vaccine development is a promising prevention strategy, and my NIH colleague will be discussing this issue. But even before the development of a vaccine, we can prevent cervical cancer in women who are already infected with HPV. For example, it may be possible to use HPV DNA tests as an adjunct to the Pap smear to improve the latter's accuracy. Studies are now underway to determine if these combined modalities would help to identify women who might otherwise be missed by Pap smear alone.

Several studies have also reported that providing HPV testing for these women can help determine who is likely to have a more serious problem, and so these tests might be combined with Pap smear screening to provide a triage of sorts to identify these individuals.

CDC is involved in a variety of research and programmatic activities related to HPV and cervical cancer. However, additional important activities must be undertaken. These include determining the clinical usefulness of HPV tests and their relative costs and benefits, developing appropriate counseling messages for women who learn that they have a cancer-associated STD, evaluating the effectiveness of various primary prevention strategies, and developing systems to track transient HPV.

Thank you for the opportunity to bring this important public health issue to your attention, and I will be glad to answer any questions that you might have.

[The prepared statement of Ronald O. Valdiserri follows:]

PREPARED STATEMENT OF RONALD O. VALDISERRI, DEPUTY DIRECTOR, NATIONAL CENTER FOR HIV, STD, AND TB PREVENTION, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

HUMAN PAPILLOMAVIRUS INFECTION AND CANCER OF THE CERVIX: WHAT DO WE KNOW AND WHAT ARE THE IMPLICATIONS?

I am Dr. Ronald O. Valdiserri, Deputy Director of the National Center for HIV, STD, and TB Prevention at the Centers for Disease Control and Prevention (CDC). Thank you for the opportunity to present what we know about the relationship between human papillomavirus (HPV) infection and cancer of the cervix which was one of the most common cancers among women in this country prior to the introduction of Pap smear screening and remains one of the most common cancers worldwide. For more than a century, there have been suspicions that cancer of the cervix is caused by an infectious agent and behaves like a sexually transmitted disease (STD). For example, epidemiologic studies have consistently shown that cervical cancer is rare in virgins but much more common in women who are sexually active and at risk for other STDs—especially so in women who became sexually active at a young age, who have multiple sexual partners, or who have sexual contact with a man who has had multiple partners.

Over the past 50 years, there have been many studies attempting to assess whether a particular infection—such as gonorrhea, syphilis, chlamydia, or genital herpes—was the sexually transmitted agent that led to cervical cancer. Many of these studies cast suspicion on one or more of these infections, but the results remained inconclusive until the 1980s when, using newly developed laboratory techniques, evidence began to point to another, less well understood, STD: the human papillomavirus or HPV. Prior to that time, HPV was known to cause non-sexually transmitted warts at body sites such as the hands or feet, as well as sexually transmitted warts around the genitals. But because warts were rarely found on the cervix, it was thought unlikely that HPV could be playing a role in causing cervical cancer. The inability to recognize cervical HPV infection was in large part due to the problem that, unlike most other STD organisms, there was and still is no way to culture HPV in the laboratory.

The development of laboratory tests for detection of HPV/DNA, the genetic material of the virus, helped to overcome this problem and dramatically increased our estimate of just how frequent HPV infection of the cervix and other genital sites actually occurs. It is now estimated that approximately 5,000,000 new cases of genital HPV infection occur in the United States each year, making it the most common of all of the STDs. It is further estimated that at least 50 percent of sexually active men and women will acquire genital HPV infection at some point and that as many as 45,000,000 Americans may already be infected. As with many STDs, most of these infections are asymptomatic, so that the majority of those with genital HPV are unaware of their infection—further contributing to its spread. The economic burden resulting from these millions of infections has not been clearly determined, but is likely quite large. One recent estimate by the Institute of Medicine was over $3 billion per year, more than that for any other STD apart from HIV infection.

The HPV DNA tests have revealed that there are many different strains or types of HPV; more than 80 types have been identified. Approximately 30 of these are found primarily in the genital area and are considered "genital HPV". While some of these 30 types are considered "low-risk," primarily causing genital warts and low-grade Pap smear abnormalities, approximately 10 of these types are considered "high-risk" for cancer in that they are found in approximately 95 percent of all tissue specimens from cervical cancer. Large epidemiologic studies comparing women with cervical cancer to those without it have shown that, even when controlling for other factors that might make cervical cancer more likely, being infected with one of these high-risk HPV types increases the risk of cervical cancer by at least 30-fold, a level similar to or higher than the risk of lung cancer from smoking. In addition to these human studies, laboratory experiments provide additional support that HPV causes cervical cancer, by showing that when inoculated into cell culture systems, HPV causes the cells to grow in an "out-of-control", cancer-like fashion and that these out-of-control cells can then cause cancer when injected into mice. Thus, while definitively proving that an infectious agent causes a disease can be quite difficult, based on a large number of studies, there is now widespread consensus among cancer researchers that high-risk types of genital HPV clearly play a causative role in the development of cervical cancer, and probably other types of anogenital cancer, such as cancer of the penis and anus.

Having HPV seems to be "necessary" for developing cervical cancer, although having the infection alone is not "sufficient" to produce cancer, and other co-factors such as smoking, an abnormal immune system, and other infections may be important as well. The role of the immune system has been most clearly demonstrated in patients with HIV infection in whom very high rates of HPV infection occur and in whom both cervical and anal cancer appear to be increased. Although a large proportion of sexually active women will become infected with genital HPV, the majority of these infections become undetectable over time without specific treatment or the development of complications. Only those women whose infection persist are at risk for developing cancer, and it has been estimated that approximately 5-10 percent of women with high-risk types of HPV infection will develop cervical cancer. Pap smear screening programs and early treatment reduces this percentage even further.

The recognition that this important cancer is caused by a highly prevalent STD has important implications for public health. The first strategy to consider is that of primary prevention, namely, preventing cancer by preventing infection. Unfortunately, the traditional STD control strategy of preventing transmission by identifying infected persons and then treating them and their partners in order to prevent transmission to other partners currently has limited value for viral STDs such as HPV because existing therapies do not cure infection. The therapies available for both genital warts and cervical HPV infection will eradicate the tissue abnormality, but probably do not eliminate the infection entirely. Abstinence should be effective for preventing HPV infections, since the large majority are sexually transmitted. However, other approaches to prevent HPV infection are also promising. Latex condoms can be expected to be protective if they cover the genital skin that is infected and if they are used consistently and correctly. Several studies have shown condoms to provide some protection against cervical cancer, and the more recently developed female condom has promise as a physical barrier in the prevention of viral STDs because of its greater surface area.

Microbicides, chemicals that inhibit microbial growth and could potentially function as "chemical barriers" also have potential benefit. Some of these agents currently under investigation have been shown to inactivate genital HPV in the laboratory. Advantages of microbicides include both the possibility of inhibiting multiple STDs—such as HPV and HIV—with one agent, and providing a protective strategy under the control of the woman, in contrast to male condoms.

The most promising primary prevention strategy would be the development of an HPV vaccine. There are several animal models in which papillomavirus infections specific to the particular animal can be effectively prevented by immunization, which has created great optimism that vaccines against HPV might be beneficial in humans as well.

Several small studies are now underway in humans to determine whether the experimental HPV vaccines are sufficiently safe and effective at producing an immune response to warrant larger, more definitive studies. Because of the relatively large number of high-risk HPV-types believed to cause cervical cancer, effective vaccines will have to contain multiple types of HPV to achieve high levels of benefit, which increases the complexity and length of time it will take to develop and test them.

Such preventive vaccines would ideally be given prior to the onset of sexual activity probably in early adolescence since most people who contract genital HPV infection do so within the first several years of sexual activity. Because the peak incidence of cervical cancer are between 35 to 55 years of age, it would likely be at least 20 years after the initiation of vaccine programs before we would see reductions in cancer rates. However, effective vaccines would also reduce the rate of pre-cancerous Pap smear abnormalities, known as dysplasia. Considering that the evaluation and treatment of dysplasia is among the most expensive aspects of the current cervical cancer prevention efforts, reductions would most likely occur much earlier in cost as well as the avoidance of anxiety that often accompanies the diagnosis of an incurable STD or pre-cancerous changes on a Pap smear.

Our current strategy is to prevent cancer in those who already have HPV infection. In essence, this is what Pap smear screening is directed toward—the early detection of pre-cancerous changes caused by HPV infection which can be evaluated and treated to prevent their progression. With the knowledge that HPV infection causes cancer, it may be possible to use HPV/DNA tests as an adjunct to the Pap smear to improve its accuracy. A single Pap smear does not identify all women who have serious abnormalities, so serial Pap smear screening is the current standard of care. Studies are underway now to find out if using HPV/DNA tests, along with the Pap smear, will increase the test sensitivity (in other words, the likelihood of identifying women with abnormal Pap smears). If these tests work well enough, they might not only prevent women with treatable problems from being missed, they might also allow Pap smears to be done less frequently than annually in most women, thereby reducing costs of screening. Furthermore, because samples for HPV testing are easier to collect than Pap smear samples, they may permit the development of self-collected swab kits for women, which, by avoiding the need for a full gynecologic exam, might be more convenient for many women and could encourage many more women to get tested for HPV. Such self-collected testing also facilitate development of outreach efforts, where field workers go into non-clinic locations to do testing, similar to approaches that have been used for community-based programs to address high blood pressure, high cholesterol, tuberculosis, and even STDs like chlamydia.

An even more immediate use of HPV tests for secondary prevention is their use to triage women with low-grade Pap smear abnormalities. Currently, the large majority of women in the United States with abnormal Pap smears have early changes that have a very low risk of progression to cancer, and yet, to be sure an important problem isn't missed, these women usually need to come back for several follow-up examinations, creating tremendous anxiety and expense. Several studies have reported that providing HPV testing for these women can help determine who is likely to have a more serious problem. If these reports can be confirmed by larger studies now underway, they may permit a more cost-effective approach to this very common problem.

Important work remains to be done before these strategies will be ready for widespread implementation. CDC is currently involved in a number of applied research and service activities to improve prevention of genital HPV infection and cervical cancer. Among these are:

- studies of the epidemiology and natural history of HPV infection and cervical cancer.
- studies to better define approaches to clinical use of HPV tests.
- studies to assess HPV-related complications in patients with HIV infection.
- studies to determine mechanisms by which HPV causes cervical cancer.
- development and assessment of improved HPV tests.
- implementation of a pilot national population-based serosurveillance study to more accurately assess the extent of genital HPV infection.
- support of health care provider training programs regarding both cervical cancer and genital HPV infection.
- development of clinical practice guidelines for genital HPV infection.
- education of the general public through the CDC National STD Hotline
- implementation of the National Breast and Cervical Cancer Early Detection Program that provides access to cancer screening and follow-up for underserved women.
- development of the National Program of Cancer Registries that will enhance surveillance of cervical and other HPV-related cancers. Currently, serious gaps in our knowledge preclude the formulation of more effective prevention strategies for genital HPV infection and cervical cancer:

HPV Testing

- If the ongoing studies to assess use of HPV tests for triage of women with low-grade Pap smear abnormalities find this to be a helpful strategy, we must determine if this approach works equally well in all groups of women. For example, because younger women have much higher background rates of HPV infection than do older women, HPV testing may be too non-specific (i.e. likely to test positive when no serious abnormality really exists) to be helpful in the younger group, and could turn out to be a "double-edged sword", creating more anxiety and costs than it saves.
- Studies to assess the use of HPV tests as an adjunct to Pap smear screening will also need to demonstrate which groups of women (such as younger vs older) get the most benefit from this extra test.
- As "self-test" kits are developed, program evaluations will be necessary to find out how best to distribute them and encourage their use. Any use of such HPV tests will require the development of approaches both to counsel women who suddenly discover that they have a cancer-associated STD, and to evaluate their sexual partners.

HPV Vaccine Development and Use

- The development of effective HPV vaccines would be enhanced by collection of additional surveillance data on the prevalence of different types of HPV infection in different groups of men and women, both to determine exactly which types of HPV a final vaccine should contain and to track early benefit of vaccines once they are licensed and widely used.
- There is virtually no experience in "marketing" vaccines for prevention of STDs and cancer to the general public or to health care providers. Yet for HPV vaccines to achieve their promise, their use will need to be as widespread in the population as is the virus. Sexually active persons in all socioeconomic groups are at risk for HPV infection; thus, immunization of all persons who will potentially be sexually active in the future would likely be the most effective prevention approach. Behavioral and social marketing research to explore this issue will be important and such research may also have benefit for other STD vaccines, including those for HIV.
- To the extent that effective HPV vaccines are developed and utilized and Pap smear abnormalities prevented, approaches used in Pap smear screening programs will also likely evolve, since criteria for what constitutes a suspicious smear may change as certain types of HPV infection are prevented.

Assessment of Non-Vaccine Strategies for Primary Prevention

- Pending the availability of effective vaccines, a better understanding of how well other primary prevention strategies may work is important. Understandably, one of the major concerns of patients diagnosed with genital HPV infection is how to prevent it from being transmitted to sexual partners, an issue that will only increase if clinical use of HPV testing becomes more widespread. To this end, better information is needed to determine how long someone with genital HPV is contagious to a sexual partner and which prevention strategies work best to prevent transmission.

Programs to Assess Burden of Infection

- Monitoring systems to provide information about rates of various types of Pap smear abnormalities and of type-specific genital HPV infections in targeted populations will be important in planning and evaluating vaccine programs, as well as in tracking the distribution of HPV infection in the population. Such studies may be particularly useful in clarifying rates and types of infections in men about which far less is known than for infections in women.
- Economic assessments of the costs resulting from HPV infection are limited and not available for all populations. Furthermore, existing analyses address only direct medical costs (the costs of actually providing care), and there is virtually no information on indirect costs (those resulting from lost productivity or premature death of someone with a medical problem) or intangible costs (such as anxiety and distress in personal relationships). Such information is critical in determining the potential public health and societal benefit of various prevention programs.

Programs to Increase Public and Health Care Provider Awareness

- While better understanding of the prevalence of HPV and its relationship to cancer will support better prevention efforts, messages to educate the general public about HPV will need to be clearly crafted to avoid undue anxiety, competition with other public health prevention messages, and the possibility because of the stigma associated with STD and undermining Pap smear screening programs.

- The issues around HPV are complex ones for health care providers who must convey messages that are both accurate and helpful to patients with concerns, often in time-constrained clinical settings. In addition, because genital HPV infection is a minor health problem for the vast majority of infected people, proper education and counseling may be as important as treatment. More cost-effective means to convey this information is an important priority.

In April, 1999, CDC and the American Cancer Society will convene a pivotal meeting of national and international experts, including our NIH colleagues, to review possible prevention strategies and prevention research needs for genital HPV infection and its complications. The goal of this meeting is to develop priorities for a linked programmatic and research agenda for CDC and other public health agencies.

Mr. BILIRAKIS. Thank you very much, Dr. Valdiserri.

Dr. Lee?

STATEMENT OF NANCY C. LEE

Ms. LEE. Good afternoon, Mr. Chairman and the subcommittee members. Can you hear me? I am Dr. Nancy Lee, Associate Director for Science at the Division of Cancer Prevention and Control at the CDC in Atlanta. I am pleased to be here this afternoon to discuss how CDC approaches cervical cancer early detection through the National Breast and Cervical Cancer Early Detection Program.

As discussed in the previous presentation, infection with certain strains of HPV is one of the strongest risk factors we know for cervical cancer. But the most important risk factor for developing cervical cancer, at least from the point of view of what we can do about it now, is the failure to receive regular screening with a Pap smear.

Cervical intraepithelial neoplasia or CIN is the pre-cancerous condition that can develop into cervical cancer. With appropriate treatment, almost all women diagnosed with CIN should be cured of their condition. From the time a women develops CIN, it usually takes years before cervical cancer develops. So we have many opportunities to detect pre-cancerous lesions with regular Pap screening, treat them, and actually prevent cervical cancer. Furthermore, even if cervical cancer has developed, when detected at its earliest stage, the 5-year survival is over 90 percent.

The accepted screening test for cervical cancer is the Pap smear. Since introduction 50 years ago, the Pap smear has been credited with the steady decline in cervical cancer deaths in the United States. In 1994, well over 90 percent of all women had received a Pap test at least once in their lives, and 80 percent had one within the preceding 3 years.

In 1990, as many of you have spoken already, Congress passed the Breast and Cervical Cancer Mortality Prevention Act. This act authorized CDC to establish a nationwide screening program to ensure that low-income women who are uninsured receive regular screening for breast and cervical cancer.

In fiscal year 1999, with appropriations of $159 million, the CDC entered into the ninth year of the National Breast and Cervical Cancer Early Detection Program. CDC supports programs in all 50 States, 5 U.S. territories, the District of Columbia, and 15 American Indian and Alaska Native organizations. The national program has provided more than 1.1 million Pap smears to over

700,000 women. However, with existing resources, it is able to screen only 12 to 15 percent of the eligible population annually. Significantly, almost half of the women screened are from minority racial and ethnic groups. This is the really good news: More than 31,000 cases of these pre-cancerous lesions have been detected and only 508 women have been diagnosed with cervical cancer.

This last set of statistics illustrates a key point that I always emphasize when I talk about the program. The main purpose of cervical cancer screening is to find pre-cancerous lesions, treat them, and cure them so that these women never have to be diagnosed with cancer.

Our program statistics illustrate the success of Pap testing and emphasize the proven strategy that can be used to fight this disease. We consider women who do not receive Pap tests to be a priority population. The national program endeavors to provide cervical cancer screening to women who are hard to reach because of cultural, language, or financial barriers. Our No. 1 goal must be to reach the largest number of unscreened women as our resources allow.

For example, many programs are involved with developing low literacy, bilingual, or culturally appropriate materials that are used in a myriad of training and outreach programs and educational campaigns. The various strategies used by different programs promote screening and increase knowledge and awareness of cervical cancer.

The Food and Drug Administration has approved three new technologies for Pap smears: ThinPrep, AutoPap and Papnet. These technologies all appear to do a somewhat better job of detecting cervical disease than conventional Pap tests. They are rapidly being adapted by laboratories nationwide and at least double the price of the conventional Pap test. However, there are concerns that the extra costs associated with these technologies will overshadow their benefits. In spite of the promise of these new technologies, the American College of Obstetricians and Gynecologists stated last year that their routine use, "could not be recommended based on costs and the lack of sufficient data demonstrating whether they reduce the incidence of or improve the survival rate for an invasive cervical cancer." The College also concluded that the main strategy should be screening women who are not receiving regular Pap tests, as they account for the majority of new cervical cancer cases each year.

CDC is committed to increasing the awareness, availability, and use of cervical cancer screening services for women. We must also work hard to screen those women who are not receiving regular screening, as they are at greatest risk for developing cervical cancer. This is the hardest part of our job, but one we cannot ignore. The national program will continue to develop strategies to find those women most in need of the lifesaving benefit of Pap smear screening.

Thanks for your interest in cervical cancer detection programs at CDC, and I, as well, am pleased to answer any questions you may have.

[The prepared statement of Nancy C. Lee follows:]

PREPARED STATEMENT OF NANCY C. LEE, ASSOCIATE DIRECTOR FOR SCIENCE, NATIONAL CENTER FOR CHRONIC DISEASE AND HEALTH PROMOTION, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Good Morning, I am Dr. Nancy Lee, Associate Director for Science, within the Division of Cancer Prevention and Control of the National Centers for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. I am pleased to be here this morning to discuss how CDC approaches cervical cancer early detection through CDC's, National Breast and Cervical Cancer Early Detection Program (NBCCEDP).

Background

Cervical cancer is nearly 100 percent preventable, yet according to the American Cancer Society, an estimated 12,800 new cases of invasive cervical cancer will be diagnosed in 1999 with about 4,800 women dying of the disease. The cervical cancer death rate declined 45 percent between the periods 1972-74 and 1992-94 and the overall incidence of the disease has decreased steadily from 14.2 per 100,000 in 1973 to 7.4 per 100,000 in 1995. This is largely attributed to the effectiveness of Pap smear screening for cervical cytology.

Even with this success, there remains significant disparities in the incidence and mortality of cervical cancer among some racial and ethnic minority women, when compared to the rate in white women. The incidence rate for all U.S. women is about 8 per 100,000; however, the highest age-adjusted incidence rate of 43 per 100,000 occurs among Vietnamese women, probably reflecting lack of appropriate screening. Incidence rates of 15 per 100,000 or higher also occur among Alaska Native, Korean, and Hispanic women. The death rate of 6.7 per 100,000 in African American women continues to be more than twice that of whites even though their incidence rate is slightly lower.

Early Detection

Cervical cancer occurs at an average age of 54; however, cervical intraepithelial neoplasia (or CIN), the precursor lesion to cervical cancer, most often occurs in much younger women. For a woman with CIN, her likelihood of survival is almost 100 percent with timely and appropriate treatment. The fact that CIN occurs at a younger age tells us that it usually takes a substantial amount of time for cervical cancer to develop. This means that screening younger women is an important strategy that actually prevents cervical cancer from ever developing. Furthermore, when cervical cancer is detected at its earliest stage, the 5-year survival rate is more than 90 percent.

Risk Factors

Studies that have identified risk factors associated with cervical cancer have shown that cervical cancer is closely linked to sexual behaviors, human papillomavirus (or HPV) infection, immunosuppressive disorders such as HIV/AIDS, as well as a failure to receive regular Pap smear screening. The sexual behaviors specifically associated with greater risk are intercourse at an early age, multiple male sexual partners, and sex with a male partner who has had multiple sexual partners. Experts agree that infection with certain strains of the HPV is one of the strongest risk factors for cervical cancer, but the most important risk factor for developing cervical cancer, at least from the point of view of what we can do about it, is the failure to receive regular screening with a Pap smear.

Screening Tests

The principal screening test for cervical cancer is the Pap smear. Since its introduction 50 years ago by Dr. Papanicolaou, the Pap smear has been widely used and is credited with the steady decline in cervical cancer deaths in the United States. Nationwide estimates from 1994 indicated that well over 90 percent of all U.S. women had received a Pap test at least once in their lives and that 80 percent had obtained one within the preceding 3 years.

Despite the ability of the Pap test to help reduce cervical cancer mortality, the test is far from 100 percent accurate. Approximately half of the inaccuracies are due to inadequate collection of the Pap smear by the health care provider and the other half are due to errors at the laboratory. Detecting a precancerous lesion such as CIN does not always mean that a cancer has been prevented because only some of the early precancerous lesions progress to cancer. Thus, the search for a more efficient means of screening for cervical cancer and precancer is ongoing.

The Food and Drug Administration has approved three new technologies for Pap smears: ThinPrep, AutoPap, and Papnet. The technologies all appear to do a somewhat better job of detecting cervical disease than conventional Pap tests. They are rapidly being adopted by laboratories nationwide and at least double the price of the conventional Pap test. However, there are concerns that the extra costs associated with these technologies will overshadow their benefits.

Two evaluations of cervical cytology were released in January: one done for the Agency for Health Care Policy and Research, and the other published in the Journal of the American Medical Association. Although the analyses were independently done, each determined that new screening technologies were cost-effective only if screening was infrequent, done every 3-4 years. They also found that the new technologies increased life expectancy by a relatively small amount compared with conventional Pap testing.

In spite of the promise of these new technologies, the American College of Obstetricians and Gynecologists stated last year that their routine use "[could] not be recommended based on costs and the lack of sufficient data demonstrating whether they reduce the incidence of or improve the survival rate from invasive cervical cancer." The college also concluded that the main focus should remain screening women who are not receiving regular screening, as they account for the majority of cervical cancer cases.

Screening Guidelines

There are several different recommendations from national, professional and governmental organizations on the frequency that women should receive a Pap test. The American Cancer Society, National Cancer Institute, American College of Obstetricians and Gynecologists, American Medical Association, American Academy of Family Physicians, and others developed a consensus agreement regarding cervical cancer screening. These organizations recommended annual Pap testing for all women who have been sexually active, or have reached the age of 18.

After three consecutive annual exams with normal findings, the Pap test could be performed less frequently at the discretion of the physician.

The U.S. Preventive Services Task Force recommends regular Pap tests for all women who are or have been sexually active, or who are 18 or older, and who have a cervix. The Pap test should be performed at least every 3 years. However, the interval for each patient should be determined by the physician, based on the woman's history of risk factors.

National Breast and Cervical Cancer Early Detection Program

Recognizing the value of appropriate cancer screening, Congress passed the Breast and Cervical Cancer Mortality Prevention Act of 1990 (Public Law 101-354). This Act authorized the Centers for Disease Control and Prevention (CDC) to establish a national screening program to ensure that low income women who are uninsured or underinsured receive regular screening for breast and cervical cancer and prompt followup when necessary. In fiscal year 1999, with Congressional appropriations of $159 million, the CDC entered into the ninth year of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). This landmark program brings critical breast and cervical cancer screening services to underserved women, including older women, women with low income, and women of racial and ethnic minorities.

CDC supports early detection programs in all 50 states, five U.S. territories, the District of Columbia, and 15 American Indian/Alaska Native organizations. The goal of the national program is to establish, expand, and improve community-based screening services for women at risk. The goal is achieved by screening medically underserved women for breast and cervical cancer, providing appropriate and timely diagnostic evaluations for women with abnormal screening tests and treatment services if needed, developing and disseminating public information and education related to the detection and control of breast and cervical cancer, improving training of health professionals in the detection of these cancers, and finally, evaluating program activities through the establishment of surveillance systems.

The program targets cervical cancer screening services to women who are hard to reach and are unlikely to seek a Pap test because of cultural, language, monetary or institutional barriers. As a major public health program, our overall concern must be to reach the largest number of unscreened, eligible women as possible. Thus, we also consider all women who do not receive regular Pap tests a priority population for the program. Currently, the national program follows cervical cancer screening guidelines that are consistent with the consensus guidelines developed by the American Cancer Society and others.

Providing cervical and breast cancer health education and outreach services is an essential component to the NBCCEDP. With technical guidance, our funded programs have developed projects that are focused on specific at-risk populations and cover a wide range of prevention and research activities. For example, many programs are involved with developing low literacy, bilingual and culturally appropriate educational materials that are used in a myriad of unique training and outreach programs and educational campaigns. These various strategies used by the different programs result in the common goal of increasing knowledge and awareness of breast and cervical cancer and promoting screening for early detection.

CDC partners with many national organizations to address issues related to breast and cervical cancer screening in priority populations. For instance, CDC funds the American Social Health Association to formulate a national model for the prevention of cervical cancer, using two counties in North Carolina as pilot sites and focusing upon economically disadvantaged Hispanic and African-American populations and women living in hard-to-reach urban and rural areas. This cervical cancer prevention project consists of developing and delivering culturally appropriate media messages, educational materials, client support services, and health education workshops in the community setting.

CDC is committed to increasing the awareness, availability and use of cervical cancer screening services for women. The main purpose of cervical cancer screening is not to find cancer, but to find precancerous lesions. Early detection and treatment of precancerous cervical lesions identified by Pap screening can actually prevent cervical cancer; thus, the success of any cervical cancer screening program depends on the early detection, case management and treatment of precancerous cervical lesions.

The breast and cervical cancer program has provided more than 1.1 million Pap test to a total of more than 700,000 women. With existing resources, the national program is able to screen 12-15 percent of the eligible population annually. Almost half of the women screened are from minority racial and ethnic groups. Of Pap tests provided, about 3 percent were abnormal; more than 31,000 cases of precancerous lesions were ultimately diagnosed, and 508 women were diagnosed with invasive cervical cancer. These statistics illustrate a key point for this essential public health program. The main purpose of cervical cancer screening is to find precancerous lesions, treat them, and cure them, so that these women do not go on to be diagnosed with cervical cancer. Of all the women diagnosed with cervical disease through our program, fewer than 2 percent actually had a diagnosis of cancer. The program has potentially averted cancer in more than 31,000 women! This underscores the success of Pap testing and emphasizes the proven strategy that we as public health practitioners can use to fight this cancer.

As mentioned earlier, the success of any cervical cancer screening program depends on the early detection and treatment of precancerous cervical lesions. But we must also work hard to screen those women who are not regularly screened elsewhere. Research has shown that they are at the greatest risk for developing cervical cancer. This is the hardest part of our job, but one we cannot ignore. The National Breast and Cervical Cancer Early Detection Program will continue to develop strategies to find those women and provide the life-saving benefit of Pap smear screening.

Thank you for your interest in the cervical cancer early detection activities at CDC. I would be pleased to answer any questions you may have.

Mr. BILIRAKIS. Thank you very much, Dr. Lee.

Dr. Lowey. Well, all right, Dr. Trimble.

STATEMENT OF EDWARD L. TRIMBLE

Mr. TRIMBLE. Good afternoon, Chairman Bilirakis and subcommittee members. Thank you for inviting us to speak today. I am an obstetrician/gynecologist and gynecologic oncologist. My responsibility at NCI is the development of a new treatment for women with gynecologic cancer.

As we have heard, cervical cancer is the third leading cause of cancer deaths for women around the world. In the United States the number of cases and deaths have dropped dramatically, primarily due to effective screening and treatment of pre-invasive disease.

As we have heard, more than 90 percent of cases are due to infection with the human papillomavirus, but the vast majority of men and women who have infection with this virus will face no adverse health consequences.

The other risk factors that have been identified include cigarette smoking, a higher number of pregnancies, lower socio-economic status, immunosuppression, multiple sexual partners, a high-risk sexual partner, and an early age of onset of sexual activity.

The treatment for pre-invasive cancer is generally surgery for those with disease confined to the cervix, and radiation therapy for women found to have cervical cancer grown beyond the cervix into the pelvic tissues. The 5-year survival rate for those with disease confined to the cervix is 90 percent compared to only 50 percent for those whose disease is found to extend beyond the cervix.

We evaluate new treatment options primarily through the NCI's Clinical Trials Cooperative Groups, which bring together doctors and nurses and patients around the country. Recently, five of these trials—conducted by the Gynecologic Oncology Group, the Southwest Oncology Group, and the Radiation Therapy Oncology Group—enrolled 1,900 women with cervical cancer. The results of these trials showed that chemotherapy given at the same time as radiation therapy improved survival and decreased the number of recurrences.

When the NCI became aware of these results, we convened a jury with doctors and a representative from the patient advocacy community to review the results. That panel voted unanimously that the National Cancer Institute should issue a clinical announcement, as Senator Mack mentioned. This announcement was sent to 14,000 physicians, was placed on the NCI website, and we also worked closely with the New England Journal of Medicine, to whom 300 manuscripts were submitted, to speed review and publication of these important results.

We continue to work through our cancer centers, through our cooperative groups, through our grantees, and through investigators at the National Institutes of Health on ways to improve treatment. We are working to see whether fertility-sparing surgery can be useful to see if we can improve our chemotherapy and radiation therapy as well as to develop vaccines against the human papillomavirus.

Dr. Lowey will address the issue of vaccine development in greater detail. We are very excited about his research and that of other investigators in the field because we have the potential that we may able to prevent initial infection with human papillomavirus as well as to improve treatment for women diagnosed with cervical cancer.

Mr. BILIRAKIS. Thank you, Dr. Trimble.

Dr. Lowey.

STATEMENT OF DOUGLAS R. LOWEY

Mr. LOWEY. Yes, good afternoon, Mr. Chairman and subcommittee members. I am Douglas Lowey. I am the Deputy Director of the Division of Basic Sciences in the National Cancer Institute and also run a research laboratory at the NIH that studies papillomaviruses. I would like to thank you for the opportunity to talk with you today about the prospects of developing a vaccine against HPV infection.

As you have already heard, cervical infection with human papillomavirus is the most common sexually transmitted infection of women. Abnormal Pap smears and pre-malignant lesions represent a manifestation of this infection, and virtually all cervical cancers arise as a consequence of infection by these viruses. In addition, there is also evidence that links HPV infection at other sites in the body to several other types of cancers.

The demonstration that pre-malignant conditions and cancers are caused by an infectious agent such as a virus implies that a safe and effective vaccine which could prevent the infection, would prevent the pre-malignant adnormalities as well as the cancers. It is also possible that a vaccine directed against the virus might have therapeutic effects. However, the history of virus vaccines indicates it is much more difficult to develop vaccines that cure established infection than to develop ones that prevent infection.

The principal message I would like to convey today is that we believe real progress is being made toward achieving the goal of developing an effective, preventive vaccine against HPVs involved in cervical cancer. My reasons for this optimism are based on vaccine studies of papillomavirus infection in animals, on early phase vaccine trials in normal human volunteers, as well as on the composition of the vaccine. Efforts to develop papillomavirus vaccines with therapeutic potential are also being pursued, as Mr. Mack mentioned in his testimony.

The preventive papillomavirus vaccine is a subunit vaccine that is made by genetic engineering techniques analogous to those used to make recombinant Hepatitis B vaccine, which is widely used in the United States and elsewhere. The preventive vaccine currently in human trials is composed of multiple copies of just a single viral protein which self-assembles to form the outer shell of the virus particle in a manner that faithfully mimics the structure of this shell in an infectious virus. However, unlike infectious virus, the virus-like particles in the vaccine are not infectious since they don't contain any papillomavirus genes. Therefore, the vaccine is unlikely to be dangerous for normal individuals.

In animal papillomavirus models, vaccination with the papillomavirus vaccine has been 90 percent to 100 percent effective in preventing infection. Several pharmaceutical companies are actively involved in the commercial development of such a vaccine.

Clinical trials are also being carried out by the National Institutes of Health. This represents a trans-NIH effort with important support from the NIH Office of Research on Women's Health, the NIH Office of Research on Minority Health, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

In humans, although only a little more than 100 individuals have thus far received the vaccine, it has been well tolerated by those individuals, and almost everyone who has received adequate doses of the vaccine has mounted a strong immunologic response against the vaccine. Such an immune response often correlates with protection against infection, but the early phase trials cannot determine whether or not the vaccine is effective. These are encouraging results. However, it remains possible that the first generation vaccine may not be as effective in people as we hope.

If additional vaccine studies in normal individuals over the next year continue to show promise regarding safety and immune response, the National Institutes of Health would plan to initiate a large-scale, placebo-controlled efficacy trial in Costa Rica, a country with high rates of cervical cancer, where the National Cancer Institute already works closely with a local research team to study HPV infection in young Costa Rican women.

An efficacy trial will take a few years to complete since the vaccine needs to be evaluated in unaffected women, and its effectiveness can only be learned after HPV has developed in a reasonable number of those women who receive the placebo. Therefore, even if the vaccine proves to be effective in trials conducted by the NIH and by pharmaceutical companies, it will take several years before the vaccine would become available to the general public.

I am grateful to you for giving me this opportunity to discuss this issue with you, and I applaud your efforts and your concerns about cervical cancer and would be happy to answer questions. Thank you.

[The prepared statement of Edward L. Trimble and Douglas R. Lowey follows:]

PREPARED STATEMENT OF EDWARD L. TRIMBLE, HEAD, SURGERY SECTION, DIVISION OF CANCER TREATMENT AND DIAGNOSIS AND DOUGLAS R. LOWY, DEPUTY DIRECTOR, DIVISION OF BASIC SCIENCES, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Good afternoon. We are Edward Trimble, M.D., Head of the Surgery Section for Division of Cancer Treatment and Diagnosis and Douglas Lowy, M.D., Deputy Director for the Division of Basic Sciences at the National Cancer Institute. It is our pleasure to appear today to discuss the progress we are making in cancer research, specifically cervical cancer research, and to discuss the importance of conveying an understanding of these advances to the American public.

We are making real progress against cancer. We measure progress against cancer in two ways: first, the increase in knowledge about cancer, and second, the reduction of the burden of this disease on people. We have made progress in both our fundamental understanding of this disease and in our efforts to prevent and treat it. This is already evident in the declining cancer incidence and death rates. Between 1990 and 1995, these rates dropped for all cancers combined and for most of the top 10 cancer sites, reversing an almost 60-year trend of increasing cancer cases and deaths in the United States.

After increasing 1.2 percent per year from 1973 to 1990, the incidence rate for all cancers combined declined an average of nearly 1 percent per year between 1990 and 1995. The incidence rates declined for most age groups, for both men and women, and for most racial and ethnic groups. The exceptions were black males, where the incidence rates continued to increase, and Asian and Pacific Islander females, where the incidence rates were level. The overall death rate declined an average of 0.5 percent a year from 1990 to 1995, with the declines greater for men than for women. The only racial and ethnic group not included in the decrease in death rates was Asian and Pacific Islander females.

From 1950 to 1970, the incidence and mortality rates of invasive cervical cancer fell impressively by more than 70 percent. From 1970 to 1995, these rates decreased by more than 40 percent. Although cervical cancer has been steadily decreasing, worldwide it is still the third most common cancer among women. About 400,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrialized nations. In 1999 an estimated 12,800 cases of invasive cervical cancer are expected to occur in the United States and approximately 4,800 women will die. We must continue our research efforts to determine the most effective ways to eliminate cervical cancer.

Recent Advances in Understanding Cancer

As we understand the nature of cancer, we understand that it is a complex set of diseases, and that the answers to cancer are related to the most fundamental mysteries of life itself. We know that cancer is not one disease, but at least 100 different diseases that share certain features. Because of this it is unlikely that one magic bullet will solve the problem.

The most remarkable progress in the past 25 years has been in our knowledge of cancer biology. We are dramatically extending our understanding of what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously, released from the controls that constrain the replication of normal cells. This transformation results from changes in the function and activity of genes. Of the approximately 100,000 genes found in the human genome, the altered activities of only a relatively small number of genes are responsible for transforming a normal, well-behaved cell into a cancer cell. Identifying these cancer genes defines the central scientific hunt in cancer biology, and opens an unprecedented window into the nature of cancer. Up until now, our detection tools have lacked the sensitivity and the specificity that we must demand if early detection is to be useful and successful. Our interventions, despite their success, have, by and large, been the result of guesswork. But now, we are at a point where we can transform our approach to cancer.

No one genetic alteration is enough to make a normal, healthy cell a cancer cell. Rather, an accumulation of changes in a relatively small number of genes during the lifetime of a cell is required. We have learned that some individuals carry a very high lifetime risk of developing cancer. This understanding has allowed us to begin describing the evolution of specific cancers from predisposition to precancer to cancer. Each cancer is ultimately defined by its particular pattern of altered and normal gene activity. This unique pattern determines the cancer's rate of growth, tendency to spread, responsiveness to hormones and therapies, and also predicts the ability of a persons immune system to recognize and respond to the cancer. Moreover, cataloging these molecular patterns will ultimately tell us how many different cancers exist, and enable us to distinguish the differences between a cancer cell and a normal cell.

We also are learning to understand the causes of cancer. Research on cancer risk—the probability that the disease will occur in a given population—is identifying populations with a significant probability of developing cancer. Because cancer is a multistage process, analysis of risk factors leads to the development of prevention and control strategies, as well as early detection methods, and in some cases more precise treatments. Epidemiologic research has identified many factors that increase cancer risk. Most of these are related to environment and lifestyle, while others are part of a person's genetic makeup. With the exception of a few genetic conditions, however, it is still not possible to predict with any degree of certainty that a person having one or more of these factors will develop cancer. This uncertainty is related to the very nature of cancer and the need for many specific alterations to accumulate in a single cell for that normal cell to be transformed into a cancer cell.

Understanding Cervical Cancer

The etiology of cervical cancer is similar throughout the world. Cervical cancer results from a series of genetic changes. The National Cancer Institute is funding numerous studies to enhance our understanding of cervical cancer. Epidemiologic studies have demonstrated that infection with human papillomavirus (HPV) is the major risk factor for development of preinvasive or invasive carcinoma of the cervix. The virus contains oncogenes that can cause genetic changes or mutations in the cells, but further changes are necessary for cancer to develop. In most women and men with HPV infection, these other genetic changes do not occur and therefore, the individuals do not develop cancer or experience other adverse health effects besides HPV infection. A large study in Costa Rica also aims to understand why common HPV infections sometimes persist and progress to cervical cancer. Ethnicity-related host factors such as immune status, genetic susceptibility markers, parity and nutrition are being studied intensively. Findings from this investigation are likely to be relevant to minority populations in the United States since the incidence and mortality rates for cancer of the cervix are two to three times higher in Hispanic and African American women compared to White women. Certain Asian American populations, especially Vietnamese women, also have high rates of cervical cancer. Ethnic differences exist mainly in women over 50 and are decreasing over time. Other known cervical cancer risk factors include long intervals since last Pap test, multiple sexual partners, cigarette smoking and higher number of births.

Cervical Cancer Screening

The majority of cervical cancers develop through a series of gradual, well-defined precancerous lesions. During this lengthy process, the abnormal tissue is easily detected by the Pap test. In the majority of women, the abnormalities will clear up without treatment, but in some instances a few of these abnormal cells will develop into cervical cancer. Early detection of the disease through the use of a Pap test is directly related to survival. The five year relative survival rate for cervical cancer is 88 percent for women with an early diagnosis of localized disease. For women initially diagnosed with later stage cervical cancer, the survival rate is only 13 percent. Studies have found that the risk of developing invasive cervical cancer is 3-10 times greater in women who have not been screened. Risk also increases with longer duration following the last normal Pap test.

Women ages 65 and older account for nearly 25 percent of cervical cancer cases and 41 percent of cervical cancer deaths in the United States. A National Health Interview Survey has shown that more than one-half of all women ages 65 and older have not had a Pap test in the past three years. The pap test is the most effective screening procedure for detecting abnormal changes in the cervix but many older women do not know how often to get a Pap test, and are unlikely to be tested regularly. Since, many older women do not get regular pap tests, the older a woman is when cervical cancer is diagnosed, the more likely she is to be diagnosed with later stage disease.

NCI is conducting a large national study to find the best way to manage the mild abnormalities that often show up on Pap tests. The study, called the ASCUS/LSIL Triage Study or ALTS is comparing three approaches: 1) immediate colposcopic exam and biopsy (the current standard); 2) repeating Pap test every six months (because most abnormalities return to normal without treatment); and 3) testing for cancer-associated types of HPV as a means to differentiate between abnormalities that need immediate colposcopy and those that can be best followed with repeat Pap tests. The final results of this study are expected in three years and could affect the 2 to 3 million American women each year who learn that their Pap test has uncovered a mildly abnormal change in cells lining the cervix.

Advances in Therapy

Despite screening, women still get cervical cancer and need therapy. Forty years ago, it was not clear that cancer, other than that which could be removed surgically, could even theoretically be cured. The first proof that cancer can be treated and cured came with childhood cancers, where survival was once measured in weeks to months and where now the great majority of children with cancer are cured. Now, for some cancers, our ability to cure is relatively predictable. For others, our ability to cure is remarkably unpredictable.

Cancer research is also improving the traditional mainstays of treatment—surgery, radiation, and chemotherapy. Clinical trials are instrumental in these improvements. Last month in an important advance notice, NCI issued a Clinical Announcement to thousands of physicians who treat cancer, describing the results of five large studies that have shown that women with invasive cervical cancer have better rates of survival when they receive chemotherapy that includes the drug cisplatin along with radiation therapy. Until last month, surgery or radiation alone had been considered standard treatment for this form of cancer. The new findings show that the risk of death from cervical cancer was decreased by 30 percent to 50 percent by combining cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer. This new approach to cancer therapy is the direct result of the Nation's clinical trials system.

Cervical Cancer Prevention

NCI is leading the development of a vaccine to prevent cervical cancer. This vaccine is based on the concept that almost all cervical cancers are caused by papillomavirus infections. (HPV type 16 has been found in more than one-half of cervical cancers, and three other types of HPV are found in another 30 percent of the tumors.) The vaccine has proven highly effective in animal trials. The vaccine is likely to be safe since it is not infectious and does not contain the potentially cancer causing viral genes. Among prevention vaccines in development, three early phase trials are in progress and being tested in people. One of these, developed at NCI in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the NIH Office of Research on Minority Health and Johns Hopkins University, has been tested in a phase I trial, and the preliminary results have been very encouraging, showing that it stimulated production of HPV antibodies and was safe. If these results are confirmed after further follow up and analysis, a full efficacy trial will test the NCI vaccine in a larger group of women in the United States and Costa Rica, leading to a full phase III trial in Costa Rica. Determining the long term efficacy of this preventative vaccine will take several years. The NCI is also working with investigators in universities and industry to develop vaccines which might improve cancer treatment.

NCI also conducts and supports research into behavioral aspects of cancer prevention. Smoking cessation is a major research priority at NCI since exposure to cigarette smoke is associated with increased rates of many cancers, including cervical.

Dietary intervention is another research priority for the institute since increased intake of certain micronutrients and other dietary factors such as carotenoids have been suggested as being associated with a decreased risk for developing cervical cancer.

Public Understanding

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate. Our programs are based upon needs identified through epidemiologic studies and market research among specific population groups, resulting in programs that are relevant and understandable to each group. Our patient education program, leadership initiatives for special populations, and minority research networks are all actively involved in spreading state-of-the-art information about cancer prevention, detection, diagnosis, treatment, and care.

The primary avenues NCI uses to communicate with the public and the health care community are:

Clinical Announcements: Important cancer research findings are released directly to the public and to the thousands of physicians who treat cancer patients through NCI's clinical announcements. Announcements of research findings are mailed directly to physicians and the national press is provided with the announcements so that they can inform the public.

World Wide Web (http://www.nci.hih.gov): Currently NCI is redesigning its web site to increase its usefulness as a communication tool. The new web site will be organized so that clinicians, researchers, and the public can quickly and easily locate up-to-the-minute information that is relevant to their needs. A new addition to NCI's Web site is the Cancer Trials site (http://www.cancertrials.ncl.gov). Through this site, patients, health care professionals, and the public can learn about ongoing NCI-sponsored trials, read about the most recent advances in cancer therapy, and explore other information resources related to cancer treatment. This web site was used by many patients and others who wanted information about treatment advances publicized over the past several months.

Cancer Information Service (CIS): The CIS provides accurate, up to date cancer information to patients and their families, the public, and health care professionals in every state through 19 offices located at NCI-funded Cancer Centers and other health care institutions. By dialing 1-800-4-CANCER, callers are automatically connected, free of charge, to the office serving their region. Information on specific cancer types, state-of-the-art care, clinical trials, and resources such as support groups or screening and smoking cessation programs is provided in English or Spanish by specialists who respond to more than 600,000 inquiries annually. The CIS regional offices are NCI's focal point for state and local cancer education efforts that target underserved, high risk, and low literacy populations.

The CIS distributes informational resources on cervical cancer free of charge. In order to reach the ethnic populations that are at increased risk for cervical cancer, NCI is collaborating with the Food and Drug Administration in distributing Pap test and cervical cancer brochures in Vietnamese, Cambodian, Samoan, Laotian, Thai, Chinese, and Korean. The CIS also distributes an intertribal video on early detection of cervical cancer for American Indian Women that was produced in conjunction with the Nebraska Department of Health.

Physician Data Query (PDQ): Patients and health care professionals want and need access to accurate, up-to-date, comprehensive information about ongoing clinical trials. Through PDQ, NCI provides information about NCI-sponsored trials. We are in the process of expanding the database, with the cooperation of patient advocates, the Food and Drug Administration, and the pharmaceutical industry, to include all cancer clinical trials approved by the FDA and to revamp the way information is presented. This system has served as a model for other institutes at the National Institutes of Health, and we want to ensure that it continues to be responsive to the needs of the communities we serve.

Medical choices are increasingly made on an individual basis, requiring that physicians and their patients have access to the resources needed to make an informed decision about their treatment and care. Communicating the importance of research findings to physicians and patients in a clear and understandable manner is central to making critical decisions about a patient's treatment and care. NCI has launched a new national media campaign on cervical cancer screening—"Pap Tests: A Healthy Habit for Life." The first phase of the campaign is focused on encouraging women, ages 65 and older, to get regular Pap tests since they continue to be at risk for cervical cancer although their screening rates decrease with age. The second phase of the campaign targets health professionals, encouraging them to continue to screen their older female patients because research has shown that general and family practitioners are not likely to screen their older female patients.

NIH Consensus Statement on Cervical Cancer: The objective of this NIH Consensus Statement is to inform physicians and the general public of the results of the 1996 NIH Consensus Development Conference on Cervical Cancer. Following established procedures, the consensus statement was prepared by a non-Federal, non-advocate, 13 member panel representing the fields of obstetrics and gynecology, gynecologic oncology, radiation oncology and epidemlolgy. The statement provides state-of-the-art information regarding preventive approaches and appropriate management of cervical cancer and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation such as: studies to assess quality-of-life issues in patients undergoing therapy for both preinvasive and invasive lesions of the cervix; research on the modification of high-risk behavior in young people to reduce the rate of HPV; research on ways to improve screening in populations that are typically underscreened such as the elderly, ethnic minorities, and the poor; and research on the development and testing of prophylactic and therapeutic vaccines against HPV.

We hope this overview provides you and the members of the committee a sense of the importance of ongoing research on cervical cancer. Thank you for your interest in the cervical cancer research activities of the NCI. We would be pleased to answer any questions.

Mr. BILIRAKIS. Thank you very much, Dr. Lowey.

In the process of trying to prepare for these hearings, we always ask that the testimony be submitted as much in advance as possible. The testimony came in from CDC, as I understand it, this morning. I know that in your particular case, we gave you plenty of notice for this hearing.

With all due respect, we would appreciate you help by submitting testimony promptly in the future.

For years, when Florida's late Governor, Lawton Chiles, was in the Senate up here, we worked together. I was a co-chairman with him on the subject of infant mortality. After discussions and research, we determined that there are adequate resources available to help reduce the very high incidence of infant mortality in this country. But, the problem was being able to get the mothers-to-be to the resources. That was a big problem. We came up with mobile sources. If we could not get them to come to us, we would go to them.

If a person qualifies for Medicaid, the program covers the Pap smear. Medicare, because of recent legislation I wrote with Mr. Brown and others, covers it now. I believe most, if not all, private insurance plans do. Now I know that there is a group of people who don't fall in those particular categories. What is the roadblock to Pap smear screening? We have determined that the early detection is so very critical. Can you address that, Dr. Valdiserri or Dr. Lee?

Ms. LEE. Yes, that is a very good question, and I think there are many barriers. There has been a lot of research in this area.

Our program particularly is targeting those women that don't have any insurance, including Medicaid. Those women are from that 40 million, and we, of course, only have funds to cover about 12 to 15 percent of that population.

The research indicates a lot of factors. It is real important that physicians and other healthcare providers take the lead in encouraging women because many women take their cue from their physicians. It is real important for us to encourage all healthcare providers to add this to the many things they are supposed to be doing.

We know that cervical cancer is highest in poor women, uninsured women, minority women, and women who are foreign-born, and women who don't receive regular healthcare.

Mr. BILIRAKIS. But, you are talking now of women who may not be well informed about the nature of this threat.

Ms. LEE. Correct. Exactly. So there are many parts of CDC's National Breast and Cervical Cancer Early Detection Program that we are trying to come in and figure out how to get those women—that is what I talked about in my testimony. That is our hard job, to get the women who nobody else can seem to get. We can pay for it, but we would have to find them.

We have given money to many primarily community-based organizations throughout the country, to farm worker organizations, migrant health, to organizations that provide services to Asian immigrants, to Hispanic and Latin American immigrants, to organizations targeting Hispanic, elderly and the elderly in the Black community. We go through churches. We go through community clinics. We have programs that fund lay health educators, and actual women who themselves have had cancer, but are not otherwise trained in the health profession to go out and witness to women about what they need to do. So, there are many strategies that we are working on identifying.

We actually have a whole set of grants now. I will conclude my answer with this: a bunch of grants to these community-based organizations take proven strategies that have been proven through good evaluation research and disseminate them into the community or different communities around the country. These are the efforts that we are trying to do to reach these women that nobody else can seem to reach.

Mr. BILIRAKIS. College women would not generally fall within the category that you described. Yet, I understand that last year the New England Journal of Medicine released a study that tracked college women at Rutgers University over a 3-year period of time and found a high incidence of HPV. So, what is the explanation, when they don't fall within that category?

Mr. VALDISERRI. Two comments on that particular study: I think that it reinforces what I said earlier in my testimony about probably as many as 50 percent of all sexually active adults in America are infected with HPV. I think that, to follow up on Dr. Lee's comments, this is an important issue that is not, unfortunately, unique to screening for cervical cancer. In fact, I remember a very interesting approach to this, looking at barriers to prenatal care, where a researcher actually went through and characterized a whole set of attitudinal barriers, informational barriers, provider barriers, system barriers, et cetera. So, to follow up on what Dr. Lee was saying, I think that there are a number of reasons why; there is no single reason why this is happening. Part of the complexity of the program and the need to do operational research is to understand what a particular barrier might be for a community of women and then to disseminate model practices to try to address that.

Mr. COBURN. Would the chairman yield for just a second a follow-up question?

Mr. BILIRAKIS. The chairman does not have much time, but go ahead.

Mr. COBURN. Your testimony that 50 percent of sexually active adults are carrying this, but, if you exclude monogamous relationships, if you include that, what you are really saying is that it is a much higher percentage in the population that is outside of the married monogamous relationships. So, that's the populations that you are studying. So, the real prevalence is much higher than 50 percent in terms of the sexually active non-monogamous relationships. Is that correct?

Mr. VALDISERRI. Well, let me, first of all, say that I don't believe that I stated that 50 percent were carrying it, because I think several of my colleagues indicated that in many instances this infection is transient. We don't know a lot about the natural history, but I think that there is a belief that in some people the infection clears, or at least it is no longer detectable.

What I did say was there are estimates that at least as many as 50 percent may have been infected by HPV. Part of the difficulty, Dr. Coburn, is that we do not have a lot of good surveillance information nor incidence information about this. I think that it is fair to say, as I mentioned, that the number of sexual partners is a clear-cut risk factor for becoming infected with HPV. So that the greater the number of sex partners, the more likely an individual would be exposed to HPV.

Mr. COBURN. Well, I thank the gentleman.

Mr. BILIRAKIS. Mr. Brown.

Mr. BROWN. Thank you.

Dr. Lee, you talked about the higher rate of cervical cancer among foreign-born women, and my understanding is that Asian-Indians, in particular, have a higher incidence, and we have talked about low-income people having high incidence. Explain why that is in all of those groups.

Ms. LEE. Maybe can I speculate some? Will you allow me?

Actually, the highest rate in recognized racial and minority groups in the country is among Vietnamese women. Alaskan Natives, Hispanics, Korean women, all have very high rates. I think a whole lot of this has to do with being recently arrived in this country perhaps from—obviously, not from Alaskan Natives, but for the Asian women and for Hispanic women from Latin and Central——

Mr. BROWN. Is it all Asian women or especially—not Indian, but especially Korean and Vietnamese?

Ms. LEE. It is mainly Southeast Asian and Vietnamese. I think Japanese women actually have a very low rate.

Mr. BROWN. And Indian women?

Ms. LEE. I have not seen the rates broken out by Indian.

Mr. BROWN. Asian-Indians, I am sorry.

Mr. LOWEY. Native American Indians.

Ms. LEE. From the subcontinent.

Mr. LOWEY. In India there is a very high incidence.

Ms. LEE. The statistics we have in this country on Asian women don't break out the Asian-Indian women.

I think that what we have found in this country is that the most profound predictor of getting cervical cancer in this country is not having screening. Okay, that does not really count in South America, for example.

Mr. BROWN. Does that account entirely for the high incidence among low-income people?

Ms. LEE. I would say in this country it is a very important thing. I am not talking about the pre-cancerous lesions because, if you are screened adequately, you are then diagnosed with pre-cancer and that is cured. The pre-cancerous lesions are also caused by HPV and the other known risk factors.

I think the primary reason that you find high rates, not the only but the primary reason, in these foreign-born and Hispanic and Asian subgroups is because they have recently arrived in this country and came from a place where they were not being screened regularly, or they are in a culture in this country where they are not getting screened regularly. That is, I think, the reason that we see the high rates in those subpopulations in this country.

Mr. BROWN. Talk more about the incidence in low-income women, please.

Ms. LEE. Now I was talking about the incidence in various racial and ethnic minority groups.

Mr. BROWN. No, I am asking you to discuss why the incidence is higher among low-income women.

Ms. LEE. I think it is among the same reasons that those women of low-income predominantly are overrepresented members in the minority community. When we look at screening data from national survey data, we are less likely to see women of low-income and low-educational status having regular Pap screening.

Mr. COBURN. [presiding] Thank you, and I will recognize myself, if I may.

First thing I would like to do is submit for the record a study that was recently published in Pediatrics about the incidence of early dysplasia and carcinoma in situ in teenagers 10 to 19, published March 3, 1999 in New England, and a ratio of 4 percent of advanced dysplasia among that group. If I have no objection, I would like to enter that into the record.

[The information referred to follows:]

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A Study of 10 296 Pediatric and Adolescent Papanicolaou Smear Diagnoses in Northern New England

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ABSTRACT. *Objective.* This study analyzes pediatric and adolescent Papanicolaou (Pap) smear diagnoses to determine the prevalence rates of squamous intraepithelial lesion (SIL) as well as infectious and reactive processes in this age group.

Design. A total of 10 296 Pap smear diagnoses from patients 10 to 19 years of age collected over a 1-year period and classified according to the Bethesda system were reviewed. This population was almost exclusively white, the majority residing in rural or suburban areas of Maine, New Hampshire, and Vermont. The percentage of abnormal smear results was then compared with data generated for older age subsets.

Results. The following diagnoses were made on 10 296 Pap smears from patients 10 to 19 years of age: 7208 (70.01%) normal; 1689 (16.4%) benign cellular change; 1004 (9.75%) atypical squamous cells of undetermined significance; 388 (3.77%) squamous intraepithelial lesion (SIL); and 7 (0.06%) atypical glandular cells of undetermined significance. A total of 1503 (14.6%) of smears showed infectious processes. Compared with the results of adult Pap smears collected over the same time period, the age 20 to 29 subset with 27 067 Pap smears and the age 30+ subset with 42 617 Pap smears showed 11.79% and 8.63% infectious processes and 3.49% and 1.27% SIL, respectively. Therefore, the highest rate of infectious processes and SIL was found in the subset of patients age 10 to 19 years.

Conclusions. Because the development of SIL and hence cervical cancer is causally related to sexually transmitted human papilloma virus (HPV) infection, this high rate of abnormal Pap smear results of both an infectious and precancerous nature in this population may reflect a high level of sexual activity among adolescent girls. These data reinforce the importance of implementing early cervical Pap smear screening in the sexually active pediatric and adolescent population. *Pediatrics* 1999;103:539–545; *Pap smears; pediatric; cervical dysplasia; adolescent; cytology.*

ABBREVIATIONS. HPV, human papilloma virus; SIL, squamous intraepithelial lesions; ASCUS, atypical squamous cells of undetermined significance; AGUS, atypical glandular cells of undetermined significance.

This study analyzes pediatric and adolescent Papanicolaou (Pap) smear diagnoses to determine the prevalence rates of cytomorphologic identifiable entities of both an infectious and precancerous nature in pediatric and adolescent girls. To the best of our knowledge, this is the largest series evaluating Pap smear diagnoses in this age group in the past decade in the United States.

The causal relationship of the sexually transmitted human papilloma virus (HPV) and squamous intraepithelial lesions (SIL) with carcinoma of the cervix has been well described.[1] Because there is a high rate of sexual activity among adolescent girls in the United States, ranging from 32.1% in 9th grade to 66.0% in 12th grade,[2] this population of girls are at a high risk for developing sexually transmitted diseases including HPV infection.

Several investigators have suggested that differences in the biologic maturity of the immune system and cervix may place adolescents at increased risk for the development of SIL. Singer[3] reported on the changes that occurred in the cervix from adolescence to menopause, noting that age, as well as sexual activity and childbirth, affected the proportion of squamous, glandular, and metaplastic cells composing the transformation zone that, in turn, may affect the susceptibility of the cervix to infection by HPV. Moscicki and associates[4] found that adolescents with SIL had a larger area of cervical ectopy (transformation zone extending to the exocervix) and were also 1 year older at menarche than were control subjects, suggesting the possibility that the biologically immature cervix with an increased area of ectopy may be

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work of Shew and colleagues proposed that a short interval between menarche and first intercourse (<18 months) is a risk factor for the HPV infection. Collectively, these data imply that a defined period of biologic vulnerability to HPV infection exists in the cervix of the sexually active adolescent, placing her at risk for the development of SIL.

MATERIALS AND METHODS

A total of 10 296 Pap smear diagnoses from patients 10 to 19 years of age collected over a 1-year period and classified according to the Bethesda system[a] were reviewed at our university-associated cytopathology laboratory. Reflecting the demographics of northern New England (Maine, New Hampshire, and Vermont), this population was almost exclusively white, with the majority of patients residing in rural or suburban areas. Cytomorphologic evidence of HPV infection as reflected in diagnostic features of SIL was evaluated (Fig 1 A, B). Because of the large size of this study and its retrospective approach, molecular evaluation of HPV ge- ates were reviewed for comparison. The Pap smears in the study group were obtained from family planning clinics (73.93%), as well as from private offices of family practice physicians and internists (7.36%), pediatricians (1.59%), gynecologists (6.88%), student health clinics (3.21%), and hospital collection sites (7.03%). Repeat SIL smears collected within the year of study included 0% of the 10- to 14-year-old group, 7.6% of the 15- to 19-year-old group, 9.1% of the 20- to 24-year-old group, and 7.8% of the 25- to 29-year-old group. In the group of patients 30 years and older, there was a 13% repeat rate for SIL diagnoses.

Pap smear results that were normal, as well as those showing shift in flora (Bethesda System terminology for a predominance of coccobacilli replacing the normal lactobacilli), Trichomonas, or fungus were diagnosed by CT (ASCP)-registered cytotechnologists. All smear results demonstrating benign cellular changes with reactive epithelial features, herpes, actinomyces, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), and SIL were reviewed by one of five American Board of Pathology-certified pathologists. Percentages of SIL and infectious processes

Fig 1. A, SIL, low grade, Papanicolaou-stained cervical smear of a 14-year-old. Original magnification, 1000×. B, SIL, high grade, Papanicolaou-stained cervical smear of a 16-year-old. Original magnification, 1000×.

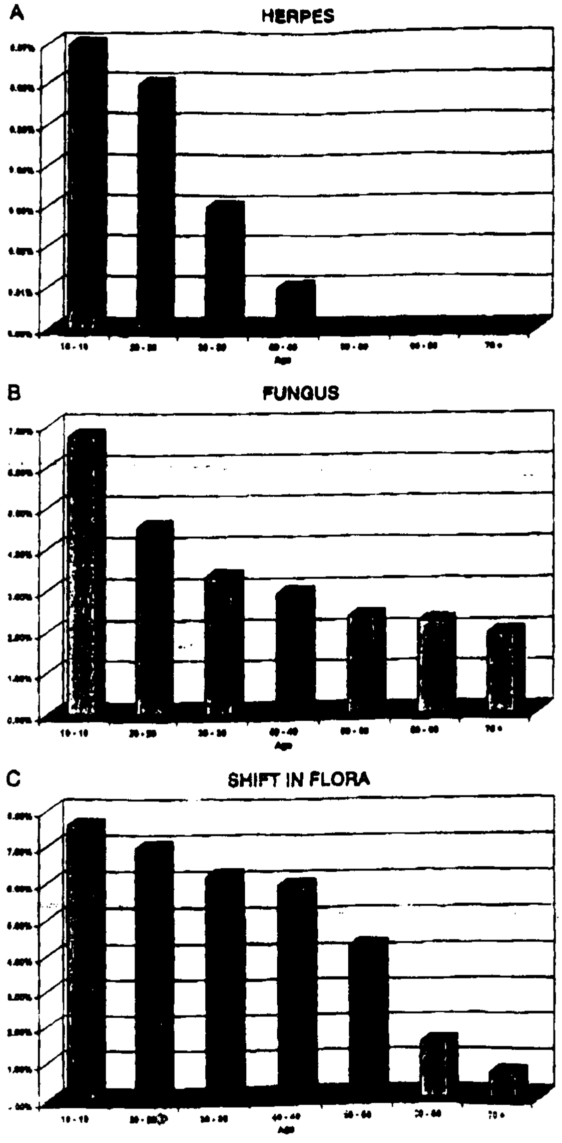


Fig 4. Percentage of specific infectious processes graphed by 10-year groupings: A, herpes; B, fungus; C, shift in flora; D, Trichomonas; E, actinomyces.

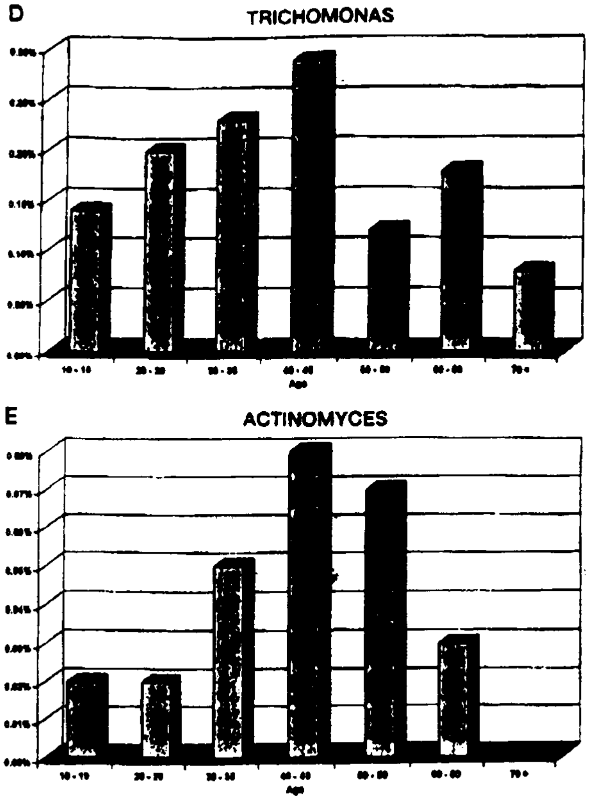


Fig 4. *Continued.*

in the pediatric/adolescent population were graphed for comparison with adults (Figs 2 and 3).

RESULTS

A total of 10 296 Pap smear diagnoses were reviewed from patients 10 to 19 years of age. There were 378 cases in the 10- to 14-year-old age group and 9918 cases in the 15- to 19-year-old age group. Normal diagnoses totaled 7208 (70.01%). Of 388 (3.77%) SIL cases, 254 were SIL low grade, 69 were SIL high grade, and 65 were SIL grade undetermined). Among the SIL cases, 7 were in the 10 to 14 age group, consisting of 5 SIL low grade (1.3%), 1 SIL high grade (0.3%), and 1 SIL grade undetermined (0.3%). There were 381 diagnoses of SIL the 15 to 19 age group, consisting of 249 SIL low grade (2.5%), 68 SIL high grade (0.7%), and 64 SIL grade undetermined (0.6%) (Fig 2, B). A total of 1004 (9.75%) cases were diagnosed as ASCUS, and 7 (0.06%) AGUS cases were identified. No cases of carcinoma were identified. Benign cellular changes numbered 1689 (16.4%), of which 1503 (14.6%) demonstrated infectious processes such as actinomyces 2 (0.02%), herpes 7 (0.07%), Trichomonas 14 (0.14%), fungus 696 (6.76%), and shift in flora 784 (7.61%) (Fig 4).

DISCUSSION

HPV is considered the most common sexually transmitted infection in both the adolescent and the adult patient.[7,8] The prevalence of HPV, however, is difficult to determine because of the varied methods for detecting the virus, which include both direct nucleic acid detection and DNA amplification techniques. In addition, different studies have used probes to different types of HPV. Reported prevalence rates for HPV in the adolescent population range from 13% to 38%.[8,9-12] Despite this broad range in prevalence of HPV, it is clear that HPV infection is a very significant sexually transmitted disease in the adolescent population.

Epidemiologic and laboratory data strongly support the association of HPV infection with precancerous SIL[13] and cervical cancer.[14] It has been estimated that between 17% and 40% of patients with molecular evidence of HPV infection will have SIL[12,15] and that as many as 80% of patients with cervical cancer have evidence of the HPV genome within the cancer as documented by either Southern hybridization or polymerase chain reaction.[16]

The rates of SIL reported in the adolescent population are complicated by differences in age groupings. For example, in our study, if we graphed our data in 5-year groups, the 20- to 24-year-old group would have the highest percentage of SIL. Clustered by decade, however, the 10- to 19-year-old population shows the highest percentage of SIL (Fig 2, A, B). Although this difference between 10- to 19-year-old groups and 20- to 29-year old groups is not statistically significant ($P = .1$), the high rates of SIL in both age groups are of clinical significance.

The distribution of the grades of SIL lesions on colposcopic biopsies from adolescents with abnormal Pap smear results (14% normal; 42% SIL low grade; 44% SIL high grade) was found to be similar to those in the adult population in a study by Jones and co-workers,[17] with the exception that no cases of invasive carcinoma were diagnosed in the adolescent group. Economos et al[18] found that 13% of the adolescents (age 14 to 19 years) with abnormal Pap smear results had histologically proven SIL high grade. In our study, which involved only cytologic diagnosis of SIL, 18% of SIL smear results had evidence of SIL high grade, 65% SIL low grade, and 17% SIL grade uncertain.

The majority of the SIL diagnoses in our adolescent population were in the low-grade category (254 cases), representing 66% of the SIL cases. This finding is of clinical significance because patients with SIL low grade are at substantially increased relative risk (more than 16-fold) of developing SIL high grade and invasive cervical carcinoma compared with the SIL-negative population.[19,20] Although most SIL low-grade lesions regress completely, the absolute risk of patients with SIL low grade for developing a SIL high grade within 2 to 4 years is 15% to 25%.[14] Furthermore, SIL high grade may arise in a HPV-infected patient without an intervening diagnosis of SIL low grade.[21]

The largest study of this nature in the United States was reported 15 years ago by Sadeghi and associates,[22] who found a 1.9% SIL rate in 194 069 sexually active adolescents (15 to 19 years of age), a figure that is less than our finding of 3.89%. In a study by Schydlower[23] of 9602 patients 12 to 21 years of age, 3% had SIL. Our data, grouped in the same manner as Schydlower's, would yield a 4.0% rate. The population studied by Sadeghi was from Cancer Screening Services in North Hollywood, CA, and thus most likely comprised urban and rural adolescents, whereas the study by Schydlower was of a military population. Despite the differences in demographics, our study of predominantly white rural and suburban adolescents suggests an increased incidence of SIL in this age group compared with these previous studies.

The explanation for this increase in SIL diagnoses is complex and hypothetic. Perhaps it reflects an increase in sexual behavior in this population. Increased detection with annual Pap smear screening and/or changes in viral types and frequencies of sexually transmitted HPV over the past decade also may contribute to the increase in diagnosis.

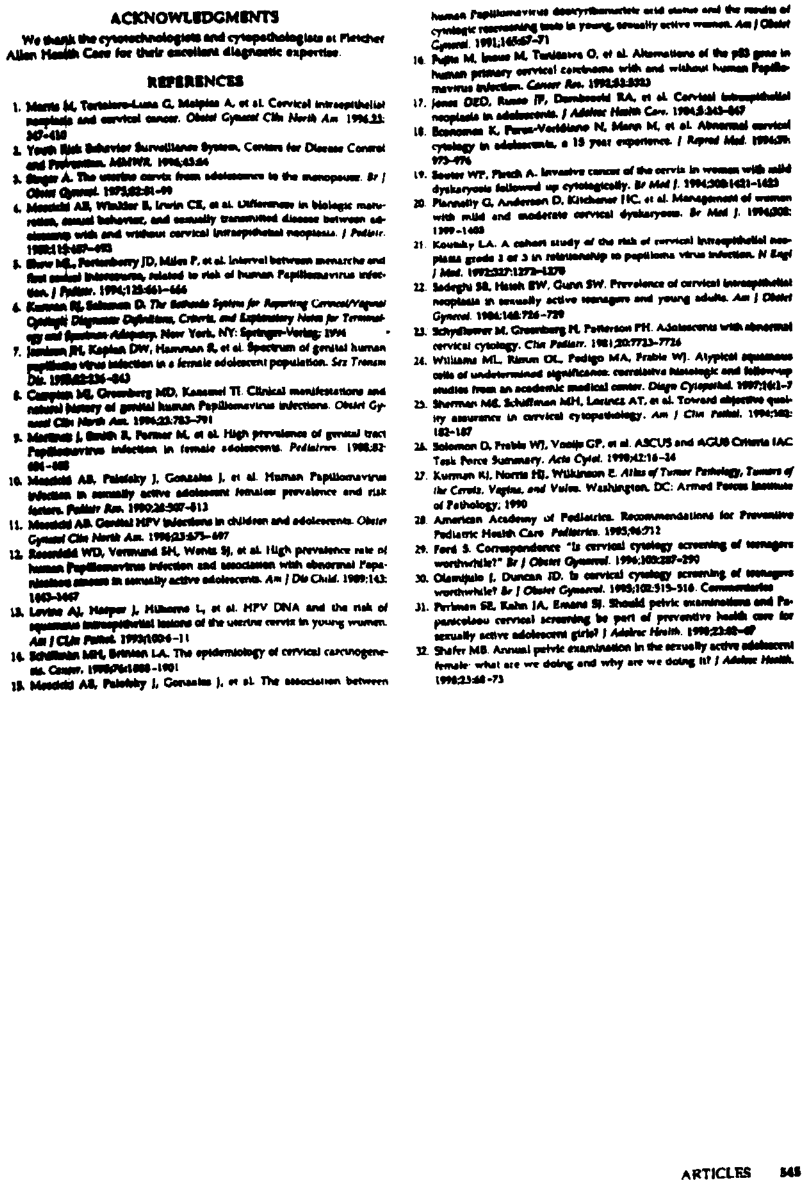
The ASCUS diagnoses, although calculated in this study, are more difficult to evaluate. Although patients with ASCUS diagnoses are at increased risk for the development of SIL,[24] the significance of this diagnosis remains, as its name suggests, "undetermined." Furthermore, ASCUS diagnoses represent the area of most intraobserver variability among cytopathologists.[24-26] The ASCUS/SIL ratio of 2.6%, however, is similar to that for adult patients at our institution.

AGUS lesions in the adolescent patient have yet to be studied in any large cohort. The Bethesda System category of AGUS includes cells of adenocarcinoma in situ as well as cells suspicious for adenocarcinoma of the cervix, which now accounts for 8% to 26% of primary cervical cancers in adults.[27]

The 14.6% rate of infectious processes, excluding HPV, was highest in the 10- to 19-year-old age cluster and when studied in 5-year groupings, showed the highest percentage in 10- to 14-year-old girls (16.7%) (Fig 3). The 10 to 19 age cluster showed the highest percentage rates of shift in flora, herpes, and fungus (Fig 4). Although not life-threatening, many of these microbiologic entities necessitate medical intervention.

The performance of a pelvic examination in sexually active adolescent girls is included in the American Academy of Pediatrics recommendations for Preventive Pediatric Health Care.[28] This recommendation states further that a pelvic examination and routine Pap smear should be offered as part of preventive health maintenance to patients between 18 and 21 years of age. The value of Pap smear examination in the sexually active adolescent continues to elicit debate as the medical economic climate forces reevaluation of many procedures previously considered routine.[29-32]

Our study demonstrates that Pap smear results from 10- to 19-year-old patients in a rural and suburban setting have the highest percentage of SIL diagnoses (3.7%) and the highest percentage of infectious processes (14.6%) of all decade groupings. The high percentage of abnormal Pap smear results reported in this study is compelling evidence for the importance of periodic cervical Pap smear screening in the pediatric and adolescent population. Based on this and other studies, we recommend strongly that sexually active girls 10 to 19 years of age undergo yearly Pap smear screening.



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Pap Smears in Adolescents: To Screen or Not to Screen?

ABBREVIATIONS. HPV, human papillomavirus; Pap, Papanicolaou (smear); ASCUS, atypical cells of undetermined significance; LG SIL, low-grade squamous intraepithelial lesion; HG SIL, high-grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion.

Genital human papillomavirus (HPV) is the most common sexually transmitted viral infection in the United States, with a prevalence of 13% to 46% in young women.[1-3] The incidence of anogenital HPV is also rising in prepubertal children, who may acquire the infection at birth or through sexual abuse. HPV has been recognized as a key factor in the pathogenesis of cervical cancer in women. The Papanicolaou (Pap) smear is an effective screening tool for cervical cancer and its precursors, and the Bethesda system, which was developed by consensus of the National Cancer Institute, is currently used for classification of Pap smears. Under the Bethesda system, epithelial cell abnormalities include atypical cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LG SIL), high-grade squamous intraepithelial lesion (HG SIL), and squamous cell carcinoma. Early detection of cervical cytologic abnormalities, particularly HG SIL, which is clearly a cancer precursor, provides the opportunity to prevent progression to cervical cancer. The relative risk for cervical cancer is 0.25 to 0.37 in women who have been screened by Pap smear compared with those who have never been screened.[4,5] Rates of abnormal cervical cytology are high among young women in the United States; a recent Centers for Disease Control and Prevention report found that in women under age 30, 8.0% of Pap smears showed ASCUS, 9.4% LG SIL, 2.1% HG SIL, and <0.1% squamous cell cancer.[6] Sexually active adolescent girls may be at higher risk for developing cervical dysplasia than older women because of early coitarche, more sexual partners, higher incidence of sexually transmitted infections, higher rate of smoking, and vulnerability of the adolescent cervix to the acquisition of sexually transmitted diseases and initiation of carcinogenesis.[7,8]

Mount and Papillo[9] have provided us with valuable new data about the incidence of abnormal Pap smears among adolescents in this issue of *Pediatrics*. They found remarkably high rates of abnormal cytology in a review of over 10 000 Pap smear results of young women in northern New England. Among those 10 to 19 years of age, just under 10% had ASCUS and 4% had squamous intraepithelial lesion (SIL). Of those with SIL, 18% had HG SIL. The 10- to 19-year-old age group demonstrated the highest incidence of SIL overall and LG SIL, and rates of HG SIL were only slightly lower than in the 20- to 29-year-old age group.

There are several methodologic issues that are important to recognize in interpreting this study and other published data pertaining to the incidence of abnormal cervical cytology. The true incidence of young women with SIL in this population is uncertain because a proportion of the Pap smears demonstrating SIL in those older than 14 years were repeat smears. The percentage of young women who presented with an abnormal Pap smear during the study period is therefore lower than the reported percentage of abnormal Pap smears. It is difficult to make comparisons between age groups because the percent of repeated SIL Pap smears differed by age: 0% of 10- to 14-year-olds, between 7.6% and 9.1% of 15- to 29-year-olds, and 13% of those older than 30. It is also difficult to compare adolescents to older women because the analyses do not control for demographic characteristics of the subjects. Certain age groups may be at higher risk for abnormal Pap smears based on demographic factors; for instance, if younger patients are more likely to come from urban areas or be recruited from family planning clinics, they might be more likely to have abnormal Pap smears. Finally, since the diagnosis of infectious agents by Pap smear is neither sensitive nor specific, specific conclusions cannot be drawn in terms of rates or distribution of infectious agents by age group.

Despite these limitations, the rates of LG SIL and HG SIL reported were strikingly high, and were likely to be at least as high in adolescents as in adults. Furthermore, a primarily white and rural or suburban population might be expected to have rates of abnormal Pap smears lower than a population of urban women of mixed race and ethnicity. The data provided in this study support the results of several other studies, which demonstrate that rates of HPV infection and abnormal cervical cytology are high in young women, and may be rising.[2,3,10,11]

Recently, there has been vigorous debate as to whether all sexually active adolescents should have routine pelvic examinations,[12,13] considering that screening for chlamydia and gonorrhea is now possible with urine testing and most cervical cytology results in adolescents are normal. We believe that data such as those presented in the article by Mount and Papillo, which demonstrate rates of abnormal cytology in adolescents at least as high, if not higher, than in adults, combined with the evidence that adolescents continue to report high rates of sexual activity, smoking and sexually transmitted diseases, argue strongly for continued Pap smear screening of all at-risk adolescents. Further research should focus on the development of innovative strategies to improve the ability to predict which adolescents are likely to develop progressive dysplasia or carcinoma in situ,[12] to most effectively prevent cervical cancer in these young women.

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Genetic Deafness: A Step Closer

Deafness from childhood is relatively common, with 1.3 per 1000 children affected,[1] but until recently the causes have been obscure. It is clear that mutations in many different genes can cause deafness, and that many of these mutations are inherited in a recessive manner. The best estimates suggest that half the cases are attributable to genetic causes and half to environmental insults,[2] but as for any disease caused by many different recessive mutations, there will be many families with a single affected child in which determination of cause is a matter of guesswork. The recent finding that mutations in a single gene, *GJB2*, encoding the connexin 26 molecule, cause childhood deafness in a large proportion of cases is set to revolutionise the field.[3-7] Not only is this gene involved in many cases of deafness, but also it is a very small gene, facilitating mutation screening, and there is one very common mutation (35delG) that can be detected by a simple laboratory test. In some populations, mutations in this gene may account for half of the cases of presumed genetic deafness. This opens up the possibility of a cost-effective molecular approach to the diagnosis of etiology in a child newly-discovered to have a hearing impairment.

In this issue of *Pediatrics*, Kimberling and his colleagues[8] describe the clinical features of a group of people with identified *GJB2* mutations. There were no distinguishing features associated with the deafness, such as inner ear malformation, thyroid or retinal defect, which might have suggested a syndrome. The authors point out that a molecular screen for a *GJB2* mutation could save the child from further diagnostic tests, some of which are invasive and expensive. Surprisingly, the extent of the hearing impairment varied from mild/moderate to profound, even within the group homozygous for the common 35delG mutation, and in some cases the hearing impairment progressed with age. This variability suggests that other factors may modify the effects of the mutation, possibly variations in another connexin gene that may compensate for the presumed inactive connexin 26 in cochlear function. From the clinician's view, the variability and possibility of progression of hearing loss are important points to consider when discussing the prognosis with the family. A subsequent child may have a more or less severe hearing impairment than the first, and any affected child should be monitored regularly in case the impairment progresses.

GJB2 is not the only gene known to be involved in deafness. Several genes for syndromic forms of deafness such as the Usher, Waardenburg, and Pendred syndromes have been known for some time. However, the bulk of childhood deafness is nonsyndromic, so there is great interest in identifying the genes responsible as a first step to devising an intervention strategy. Since the report of the involvement of *GJB2* in deafness just under 2 years ago, no less than 11 further genes have been found to be involved in nonsyndromic deafness, 1 of them another connexin gene.[9,10] As DNA screening costs are reduced and our knowledge of the responsible genes increases, it can not be long before molecular diagnosis for a broad range of deafness genes becomes available to the clinician. The debate about what to do with this information should begin now.

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Mr. COBURN. I want to spend just a few minutes going through this. Dr. Valdiserri, you have stated that there are 45 million people perhaps that have been exposed to this virus or this combination of viruses. We know that it accounts for somewhere above 90 percent of invasive cervical cancer. We have not talked about the tremendous outbreak and tremendous epidemic increase in cervical dysplasia in this country that we are seeing. Would you care to comment on that?

Mr. VALDISERRI. I don't know that I am the best person to comment on that particular aspect of it. From my focus at CDC, in my center we are not doing surveillance on cervical dysplasia. In fact, we have a meeting scheduled in early April with the American Cancer Society and colleagues from NIH and other colleagues at CDC to consider a whole host of issues around HPV, and surveillance will be one of the considerations. But I think that when we are talking about surveillance in that context, we are talking primarily about HPV surveillance.

Mr. COBURN. That leads me back to my next question.

You said in your verbal statement—and I have read your written statement—that we have data that says perhaps this may be a short-lived infection. Would you care to submit for this committee all the scientific data that you say are the studies, the peer-reviewed studies, that are out there that would say that this is short-lived, and that we can actually have for us to look at the experience model that you are calling on, to give us that information?

Mr. VALDISERRI. Let me state for the record, Dr. Coburn, that I am here as a representative of the National Center for HIV, STD, and TB Prevention. My particular expertise is not in human papillomavirus. I don't know if that was a rhetorical question.

Mr. COBURN. No, it really was not.

Mr. VALDISERRI. But, through my reading and through my discussions with some of the experts that we have at CDC, let me say, first of all, there is much that we don't know about the natural history of HPV. There are many, many issues——

Mr. COBURN. Right, but let me interrupt you there because that is exactly where I am going. My whole point is this is the largest sexually transmitted disease that we have in the country. It affects more people. It accounts for 90 percent of the cervical cancer. My question to you is, why is not a reportable disease?

Mr. VALDISERRI. Let me answer that one. But, let me go back to your first question about why I mentioned that some experts indicate that this might be short-lived. I think that that is a reflection of the fact that there is good evidence to show, although there is not incidence data, there are many, many studies showing the widespread prevalence of HPV, and this is linked with the fact that clinically, as my colleague from NCI stated as well, fortunately, for most men and women who are infected, this is a benign condition that does not even result in any kind of symptomatic presentation.

So, I think to go back to your first question, that is why some of the experts in the field, they don't know for certain, but think that this may be a short-lived condition.

Your second question, I am sorry now, I have forgotten it.

Mr. COBURN. Why is it not a reportable disease?

Mr. VALDISERRI. Why is it not reportable? There are two ways to answer that. I guess the more direct is that, as you well know, reportable diseases are determined by States.

Mr. COBURN. As I know, the CDC has a list of 53, I believe, that mandate to the States to report them of which some of their funding is dependent upon whether or not they report.

Mr. VALDISERRI. That's not my understanding of the way it works out in terms of the Federal and State relations.

Mr. COBURN. Then let me rephrase the question. Why is the CDC not making a recommendation that this be a reportable disease?

Mr. VALDISERRI. That is what I thought you might be driving at. Let me say, first of all, at CDC we would like to go on record saying that we would clearly like to have additional surveillance information about HPV, for a number of reasons.

Mr. COBURN. I am going to interrupt just for a minute. Here is the No. 1 cause of cervical cancer in the country. Five thousand women, at least, a year are dying from it. It is a known etiologic agent. It can be identified. It can be prevented with screening. Why would we not want the Center for Disease Control to make a recommendation that this is a reportable disease? Answer that from a logical conclusion.

Mr. VALDISERRI. Well, I think there are a number of reasons why there would be difficulties, in that if a State determined that it wanted to make a law reporting HPV, first of all, what test would we use? Would people use abnormal Pap smears as what constitutes the reporting condition? Given that most instances of HPV infection, as you well know, are asymptomatic and don't result in any kind of——

Mr. COBURN. Dr. Valdiserri, my point is that every day when I am in my practice, I am telling a women she has a cervical dysplasia and I am explaining to her how she got that. She got it because somebody gave her human papillomavirus. And, if I don't follow my obligation as a physician to say you have a disease that is transmissible—it is 300 times more transmissible than HIV.

Now, to tell me that I should not make that a reportable disease, that she should not inform her partners—we recently had the American College of Pediatricians come out and say we should not circumcise young men, but they totally ignored human papillomavirus and the disease characteristics that we are getting ready to see with cancer of the penis.

Mr. VALDISERRI. First of all, we don't tell individuals who are infected with HPV and have clinical manifestations and know that they are infected that they should not inform their partners. That is a misperception.

Mr. COBURN. No, I did not say that.

Mr. VALDISERRI. Well, I want to go on record saying that.

Mr. COBURN. But, if it is a reportable disease, then it becomes an obligation on the part of the physician to do what we all know——

Mr. VALDISERRI. If he or she can report it. What I am trying to get in the record is that there are some difficulties with the one family of tests that are available. My understanding is that they don't identify all the viral subtypes.

Mr. COBURN. Absolutely not; they don't. You are right.

Mr. VALDISERRI. That is correct, and we also went on record saying that there are a lot of questions about, what does antibody mean? Do people have antibody or not?

Mr. COBURN. We will spar back and forth here for a minute, but we also know that they DNA probes for chlamydia and gonorrhea are not 100 percent accurate either, but we still report those diseases.

Mr. VALDISERRI. Not in every State.

Mr. COBURN. Well, in most States they are reportable diseases. I will yield back my time and then I will ask for additional time when we finish. The gentlelady from California.

Mrs. CAPPS. I want to go back a little, although this part of what I want to say is not really a question, because I found the original discussion, after you made your testimonies and throughout your testimonies, to be so much about basic healthcare and health education. And, as a school nurse, it just resonates with me my bias about cervical cancer, so highly treatable, so easily preventable, with all these questions about why aren't women who are poor, who are born in other countries, and then we are talking about all the barriers to access, and it comes right back to people who should be talking. We should be talking about this with our well-child clinic care providers, pediatricians, and those who work with young families, because the next generation starts in utero, as was mentioned, in terms of the risk factors, but, also, for the education that must go on until we get a climate of being comfortable seeking help, particularly, when it comes to sexually transmitted diseases. And, we have a lot of discussing to do about how we can get to that point in terms of healthcare—such preventive healthcare, family oriented, really supporting families at a critical time and young people, and that is why I am delighted that we are having this hearing.

I hope that we can continue that conversation, and that whatever we can do here on the Hill to help get some of those barriers eliminated in our communities—and I am intrigued by the models that you are using. I would like to find ways to lift those out, and the ones that work, we should be doing everywhere because they are not costly. I know that it is mostly working neighborhood to neighborhood using peers and survivors, or whatever, the ways that you have found to work.

Mr. VALDISERRI. May I make just a statement? I think that is such an important point, because when we think about an infectious disease process or an infectious disease-related cancer like we are talking about here, we obviously focus on the basic research, which is fundamentally important. But, there are a whole host of operational and health services research questions like the ones that you have alluded to and like to ones that Dr. Lee mentioned that I think are extremely important that have to take place, sometimes even after some of the basic research questions have been answered. So, I appreciate your bringing that point up.

Mrs. CAPPS. Then, just one final note on that: You are coming here to the House of Representatives. Each of us has local constituencies that we represent of interest to you all, and what you do, the health of our communities depends on getting this information out. So, that is how I would like to see this conversation move forward.

What are some of the ways we can help you get the word out, try new models, and also, what can we bring to you from our communities in terms of either barriers or models for achieving success in this area?

I think what we have in the situation with cancer of the cervix is such an example. It is like a symbol of the good—it is treatable. There is a low-cost screening technique that is widely available, and yet, why are so few women taking advantage of the opportunity? So, that's to be discussed.

One quick one for me: A couple of you alluded to smoking and the relationship and I am curious. Just a couple of words about why.

Mr. TRIMBLE. Smoking appears to increase the risk of a number of epithelial of skin cancers. So we all are now aware of the association between smoking and lung cancer. But, it also increases the risk of cancer of the head and neck, cancer of the esophagus, cancer of the vulva, cancer of the vagina, cancer of the cervix.

Mrs. CAPPS. Is there a particular way that this is easily explained to the lay public?

Mr. TRIMBLE. No.

Mrs. CAPPS. No. The linkage?

Mr. TRIMBLE. Well, we don't fully understand the mechanism by which cigarette smoking does increase these risks. We note, though, that cotinine, which is one of the byproducts of nicotine, is found expressed in the cervical mucus after a person smoked a cigarette, but we don't know the specific mechanism for each of the cancers.

Mrs. CAPPS. I think we need to disseminate that information as well.

Mr. VALDISERRI. And, I mentioned smoking as an epidemiologic factor in HPV infection, but that has not been as consistent a finding as smoking in cervical cancer.

Mrs. CAPPS. Thank you very much. Thank you for being here today.

Yield back the balance of my time.

Mr. COBURN. Thank you, and the gentleman from Pennsylvania is recognized.

Mr. GREENWOOD. Thank you, Mr. Chairman.

I want to do what Senator Mack did and take off all my hats, except leave my daddy hat on. My little girls are just about to be 12, Katie is, and Laura is 13½. They are not sexually active. They will be someday. I have encouraged them to wait until after menopause, but I don't think that I am going to succeed there.

Mr. COBURN. If the gentleman would yield, there is a study that shows the incidence of cervical cancer in nuns is zero.

Mr. GREENWOOD. Nuns. Cervical cancer is zero among nuns. That is another option for them that I will encourage.

But, realistically, what we just heard about these rates of 43 percent among college coeds, I can assume that if one of my daughters is off at a college campus and becomes sexually active, that there is an extraordinarily high likelihood, particularly if she had more than one partner, if half the guys out there have HPV, and she would have two partners over the course of 4 years of college, virtually 100 percent likelihood that she gets a disease that is a very strong precursor to a very deadly cancer.

I would be happy to be corrected if my assumptions there need to be corrected. But, I think, whether they do or not, the fact is that young people today, being sexually active, as the huge percentage are, are enormously at-risk for disease that is enormously deadly.

I would guess that if you went to any college campus, go to the best Ivy League campus in the country and ask male and female college students about HPV; I would guess that an extraordinarily small percentage of them have ever heard of it, know what it means, know how common it is among their fellow students and their potential sexual partners—let alone have knowledge of the fact that it is essentially incurable, and let alone that it is a precursor to cancer which is fatal.

I have two questions: One, is there any other disease out there that is as widespread, as incurable, and is potentially devastating as this one? That is my first question. My second question is: Two, what are you doing to inform the American public, particularly the young sexually active Americans, that every time they get in bed with somebody it is a loaded gun?

Mr. VALDISERRI. Let me start out, and I suspect that my colleagues will want to comment as well.

First of all, in answering your first question, I guess I would ask you to remember, although we are dealing with an extremely serious situation here, that most instances of HPV infection are benign and don't result in cervical cancer. I am not trying minimize——

Mr. COBURN. If the gentleman would yield, I would like for you to submit to the committee the scientific peer review data that says that, because I can't find a whole lot of it.

Mr. VALDISERRI. Yes, that is not a problem. There is also a very good summary in the new STD text that came out that has hundreds of references that tell what we know about natural history. So, we can do that.

Mr. GREENWOOD. Just since I am not a physician in this triangle here, when you say most cases are benign, tell me what you mean by that.

Mr. VALDISERRI. What I mean is that, based on the evidence that we've accumulated, there are specific subtypes, specific types of the virus that are associated with cancer and specific types of the virus that are not, and maybe my colleagues from NIH and NCI can speak to this, but, epidemiologically, the estimates that I have seen are that about 5 to 10 percent perhaps of women who are infected with the so-called high-risk or the cancer-associated viruses will go on to develop cervical cancer if there is not the screening that detects the pre-cancerous lesions.

Again, that is not to minimize that percentage, because it is a tragedy each and every time it happens. But, it is important to keep that in mind when you think about how widespread this viral infection is in the population.

I think your second point is perhaps a little easier to talk to. You may be aware of the fact that the Institute of Medicine published a report on sexually transmissible diseases in America, I guess it has been about 2 years ago now, and they called it "The Hidden Epidemic." They talked about this whole issue of all of the sexually transmissible diseases that confront sexually active individuals, and I would just like to go on record saying that you are absolutely right; that we do have to get this information out there and it is one of the reasons it is important to stress to individuals that there are a lot of health benefits that derive from delaying sexual activity. But we also know that sooner or later people will become sexually active, and then we have to also provide, to the best of our knowledge, information about prevention in that context as well.

Mr. GREENWOOD. The one part of the question that I did not get a response to yet was: Is there any other disease that is this prevalent? For 50 percent of at least a subset of the population that is sexually active, for that population to have a particular virus, I can't——

Mr. VALDISERRI. Off the top of my head, I don't know, and I think it reflects the fact that the target organ for HPV is skin, an epidermal surface, and that's a pretty big target organ; there are a lot of types of them.

Ms. LEE. Let me say that once infected is not the same as having the disease; Okay? So, like, I had the flu last year, and if you went back and you were able to check those antibodies, I would have it, but that does not mean I am now affected by it. Let me just say that let's look at the positive of this. Unlike most cancers, we have a test that works, and we have dropped the rate of cervical cancer by 70 percent in the last 50 years. And so, most women who are infected with the bad kind of HPV virus, and, in fact, go on to develop these neoplastic or pre-cancerous changes, can be, and are, detected before they ever get cancer, treated in the physician's office as an outpatient. Dr. Coburn can do it. They never have to do the hospital. They don't have to get a hysterectomy. They can still have children, and then they go on. So, we can put a good, positive spin on this for this kind of cancer.

Mr. GREENWOOD. We shouldn't put any spin on it at all, but my time is out.

Mr. COBURN. Next, I'd like to recognize the gentlelady from California.

Before I do that, I would like unanimous consent to put into the record a letter from Dr. Clausner, from NIH Public Health Service, dated February 19, to the chairman, in relationship to questions that were asked by the committee—I believe you all had a copy of this letter—and also a study published in the New England Journal of Medicine on the natural history of cervical—I will make sure that you have it—cervical vaginal papilloma virus infection in young women.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
BETHESDA, MARYLAND
February 19, 1999

The Honorable TOM BLILEY, JR.
House of Representatives
Washington, D.C. 20515

DEAR MR. BLILEY: I am responding to your letter of January 12, 1999, in which you pose fifteen questions about the possible relationship of induced abortion to breast cancer, the relationship between human papillomavirus (HPV) and cervical cancer, and the National Cancer Institute's (NCI) dissemination of research findings on these topics. I regret that I could not meet your request to provide a response by January 29, 1999. My staff have worked closely with Mr. Marc Wheat to keep him informed of our progress.

As requested, the questions have been restated below. The answer follows each numbered question.

1. At the July 20 hearing on "The State of Cancer Research," the National Cancer Institute testimony addressed the importance of epidemiologic research in identifying the factors that increase cancer risk. How much of the NCI budget is allocated to the funding of intramural and extramural epidemiologic studies done for that purpose?

NCI funds the bulk of this research through the Division of Cancer Epidemiology and Genetics (an estimated *$60 million for intramural epidemiologic studies*) and the Division of Cancer Control and Population Sciences (an *estimated $147 million for extramural researchers*). Additional funding from other NCI Divisions may be relevant, but we included only projects that are directly related to studying factors that increase cancer risk.

2. NCI has a long-standing focus on "preventable causes." Are there preventable causes for breast cancer that have been identified by NCI? What preventable causes have been identified for cervical cancer?

After discussion with Mr. Mark Wheat of your staff, "preventable" (for the purpose of this inquiry) exposures are those created by human intervention; i.e., herbicides, diet. In contrast, "unavoidable" exposures are those that occur in nature; i.e., genetics.

Breast Cancer

The leading known risk factors for breast cancer are largely unavoidable. *Age* is the leading risk factor, with incidence rates increasing dramatically after age 50. Family history is a strong risk factor, particularly if a woman's mother or sister has the disease. *Genetic factors* play an important role. About 50 percent of women with a mutation in the BRCA-1 gene will develop breast cancer by age 70. It is important to keep in mind that only between 5 and 10 percent of *all* breast cancers appear to be attributable to an inherited genetic mutation. Some *benign breast diseases* increase risk, and a *previous diagnosis of breast, ovarian or endometrial cancer* is associated with risk.

Reproductive events are a strong determinant of subsequent breast cancer risk. *Early menarche* and *late menopause* increase risk, while removal of both ovaries before menopause reduces risk. Having *additional births* after the first is associated with a slightly reduced risk. The most consistent reproductive factor is the *woman's age at first full-term pregnancy.* Women without children and women having their first child after age 30 have a two- to three-fold increased risk of this disease, compared with women who give birth before age 20. A woman with an interrupted first pregnancy, either spontaneously or through induced abortion, does not reap the protective benefit of a full-term pregnancy.

Other risk factors may be considered "preventable." Taking *oral contraceptives* may increase risk for breast cancer at an early age (before age 45), and *estrogen replacement therapy* may slightly increase risk of breast cancer. Among postmenopausal women, risk increases with *weight, body mass,* and *distribution of weight.* The association with *dietary fat* consumption is inconclusive, while recent studies have shown a fairly consistent though small effect of *alcohol* consumption on breast cancer risk. Exposure to *high doses of radiation* increases risk, although the effects of low-dose radiation are considered minimal.

Most of these "established" risk factors for breast cancer are associated with only a moderately increased risk, suggesting that multiple factors may play a role in each woman's disease, and that unrecognized factors may exist. Further research is necessary, is ongoing, and remains a high priority for the NCI.

Cervical Cancer

Sexual behavior has been identified as the major risk factor for cervical cancer. Risk is increased by *early age at first intercourse* or *numerous life-time sexual partners.* The greater the number of sexual partners, the greater the risk of *sexually transmitted disease,* which can be a risk factor. Abundant laboratory and clinical data support a role for *human papillomavirus (HPV)* in cervical cancer. *Cigarette smoking* is associated with increased risk. *Barrier methods of contraception* reduce risk, and the use of *oral contraceptives* increases risk. Giving *birth multiple times* is an independent risk factor, and vitamin C, beta carotene, or folacin (one of the B complex vitamins) *deficiencies* may increase risk.

3. The NIH written testimony for the July 20 hearing states that "communicating with . . . individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate." To that end, NCI has identified preventable target exposures of cancer-causing agents as a key element in the prevention of cancer. What work has NCI done to coordinate a Federal response to the prevention of breast and cervical cancer? Specifically, what work has NCI done with the Department of Health and Human Services Office of Population Affairs and the HHS Health Resources and Services Administration to alert women to avoidable exposure to carcinogenic agents? Who are the liaisons within NCI, HRSA, and the Office of Population Affairs? Has NCI coordinated activity with the Title V and Title XX programs within those agencies.?

Federal agencies are designated to serve the United States in specific ways. The National Institutes of Health (NIH), of which NCI is a part, is a research agency. In its mission to protect and improve human health, the NIH (and NCI) conducts and supports basic, applied, and clinical and health services research to understand the processes underlying human health and to acquire new knowledge to help prevent, diagnose, and treat human diseases and disabilities. This may include *developing an information campaign* (such as the **5 A Day Program** described below, which was based on scientific evidence that increasing consumption of fruits and vegetables reduces cancer risk) and *evaluating its effectiveness* at achieving its goal (increasing the daily intake of fruits and vegetables). NCI also has a mandate to disseminate research findings so that when the development and evaluation are completed, other Federal and state agencies, and private sector organizations, may take this information and apply it accordingly. NCI, therefore, plays an integral role in these activities. For example, the Steering Committee for the National Action Plan on Breast Cancer (NAPBC) includes NCI staff as members and working group chairpersons serving this unique public/private trans-Federal partnership.

The NCI disseminates research findings widely through scientific publications, press conferences, press statements, clinical alerts, patient education materials, meetings of professional societies, television and radio, the World Wide Web, our toll-free Cancer Information Service, our PDQ databases, and the Information Associates Program. Our staff has many contacts within agencies for a variety of programs and issues. Through these personal contacts, and those mechanisms mentioned above, Federal agencies and offices have direct access to information pertinent to their programs. In addition, we maintain and foster close working relationships with other Institutes that have formal collaborative relationships with the Office of Population Affairs—our projects and programs are thus included in that broad knowledge base. NCI has several partnerships with other federal agencies and non-federal groups to enhance our information dissemination activities.

NCI has not formally collaborated specifically on Title V (Substance Abuse and Mental Health Services Administration) or Title XX (Adolescent Family Life Demonstration Projects) programs. As a research agency, NCI's role is to conduct and support research, then disseminate widely new knowledge gained. Following are examples of specific information campaigns:

- **Mammography Screening**—Scientific evidence supports NCI's recommendation that lives can be saved if women in their forties or older have regular screening mammograms, every one to two years. Because this constituted a major change in the level of scientific evidence to support screening mammography, it was imperative that NCI disseminate this information widely. Specific information targeting various populations and constituencies was developed and disseminated using a variety of mechanisms, such as patient-oriented publications, education materials, public service announcements, and electronic media.
- **5 A Day**—Because fruit and vegetable intake has been clearly demonstrated to provide a health benefit beyond cancer prevention, increasing American con-

sumption has tremendous potential to improve our Nation's health. Because health messages can be confusing, NCI set aside special funds for grantees to find innovative ways to inform the public. In an unprecedented public/private partnership, grantees and health departments nationwide participated in a study of new methods to reach the public and influence behavior. These grants are completed, and NCI and the Centers for Disease Control and Prevention (CDC) are evaluating their success. If indeed Americans increased their consumption, then other public and private groups will have scientifically proven methods to bring into their communities.

- **"Risk Disk"**—The Breast Cancer Risk Assessment Tool is a computer program that women and their health care providers can use to estimate a woman's risk of developing breast cancer for two time periods—over the next five years and for her lifetime—based on several recognized risk factors (see Question 2 for a discussion of some of those risk factors). The tool compares these risks (given as a percentage) to those of a woman of the same age with no risk factors other than her age, and with the risk of women who were eligible to participate in the breast cancer prevention trial using tamoxifen.

4. The July 20 NCI written testimony states that "NCI is actively pursuing development of a vaccine to prevent cervical cancer . . . based on the concept that almost all cervical cancers are caused, at least in part, by papilloma virus infections.' What is the status of the development of a vaccine for this disease? How long will it be before a vaccine enters clinical trials? Have any private sector entities partnered with NCI in the development of this vaccine?

The vaccine is currently being developed in clinical trials. The Phase I study to determine if the vaccine can prevent infection is underway at Johns Hopkins University, and preliminary results based on laboratory tests are encouraging—with no toxicities yet reported. Following completion of the Phase I trial, a Phase II trial to determine correct dosage is expected to begin in January 2000. A planned Phase III randomized clinical trial involving 10,000 women to test the efficacy of preventing HPV (Type 16) infection is expected to begin in about 2.5 years. As in many of our drug studies, we have partnered with a company to manufacture the virus-like particle contained within the vaccine. The manufacturer will have no role in the evaluation of its benefit or safety.

5. Earlier this year, the New England Journal of Medicine published the results of a study on human papillomavirus (HPV). Among sexually active female students at Rutgers University, approximately 60 percent tested positive for HPV at some time during the three-year study period. Given that HPV is an agent of most cervical cancer cases, which kill nearly as many women each year as AIDS, what does a 60 percent infection rate suggest to NCI about the long-term consequences of this virus? Does this infection rate suggest that condom usage is less effective at preventing HPV infection than it is in preventing pregnancy? Has NCI sponsored any research as to the effectiveness of condoms to prevent the transmission of HPV?

Experts estimate that as many as 24 million Americans are infected with HPV, and the frequency of infection and disease appears to be increasing. For most women, HPV does not remain in the body. After initial infection, most women's immune system can clear the virus within 18 months. Therefore, a high prevalence at a point in time is not indicative of the numbers of women who will suffer health consequences. In fact, most women suffer no serious health problems as a result of HPV infection, nor do they know they have been infected. Although most HPV infections do not progress to cancer, it is important for women to have regular Pap smears. Potentially precancerous cervical disease is readily treatable. By identifying women with persistent infection through screening, and then treating those with precancerous conditions (by removing the precancerous cervical tissue affected), we relieve most of the burden of cervical cancer from HPV infection in the United States.

Condoms are ineffective against HPV because the virus is prevalent not only in mucosal tissue (genitalia) but also on dry skin of the surrounding abdomen and groin, and it can migrate from those areas into the vagina and the cervix. Additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted. However, condom use is extremely important for preventing the transmission of other sexually transmitted diseases, and in the prevention of pregnancy. We include the use of condoms as an option in clinical trials if methods of birth control or disease prevention are needed.

6. What is the amount of research dollars expended on HPV as compared to the virus that causes AIDS? What is the ratio between the two research

budgets as compared to the number of women who die of the respective viruses?

There are over 80 types of HPV, about 15 of which are associated with cancer of the cervix. NCI estimates that it will spend about $38 million on cervical cancer-related HPV research, and about $235 million on AIDS-related cancers, in FY 1999.

There are about 5,000 deaths in the U.S. from cervical cancer each year, and more than 200,000 deaths world wide. Over 90 percent of these cancers are HPV-related. There were about 4,600 female deaths in the U.S., and 900,000 worldwide, from HIV-related illness in FY 1997.

7. What action does NCI recommend be undertaken by the Federal government to address the public health threats of HPV?

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease in the world. The NCI believes that if all women had pelvic exams and Pap tests regularly, most precancerous conditions would be detected and treated before cancer develops. At present, early detection and treatment of precancerous tissue remain the most effective ways of preventing cervical cancer. This is communicated in our publications and public information. NCI is working to develop a vaccine that will prevent the main cancer-causing types of HPV, and is investigating the use of HPV testing, via more accurate Pap testing programs, to improve cervical cancer screening and prevention.

8. According to an Associated Press report on a Supreme Court ruling dated January, 11, 1999, HHS had a hand in the removal of controversial posters in the Philadelphia public transit authority that linked abortion to breast cancer. According to this report, in "Early February [1996], the authority received a copy of a letter a federal health official had sent to the Washington Metropolitan Area Transit Authority. Dr. Philip Lee, Assistant Secretary of Health in the Department of Health and Human Services, called the anti-abortion ad 'unfortunately misleading' and 'unduly alarming,' and said it 'does not accurately reflect the weight of the scientific literature.' Based on Lee's letter, SEPTA removed the posters on Feb. 16, 1996." Please provide the Committee with a copy of this letter, and copies of all other letters HHS has sent since 1993 raising concerns about ads making cancer claims that may be "unduly alarming." On what basis was the ad found to be "unfortunately misleading," "unduly alarming," and that it "does not accurately reflect the weight of the scientific literature"?

In early 1996, NCI staff drafted a response to requests for information about the scientific evidence concerning the relationship between induced abortion and breast cancer risk. The letter was drafted for Dr. Klausner's signature (**Attachment 1**), but there are no copies of other drafts, or of correspondence to SEPTA, signed by either Dr. Klausner or Dr. Lee in NCI's central files system or with queried staff. There were several meetings with Dr. Lee and/or members of his staff to discuss a response. We have suggested to Mr. Wheat that he ask the Department of Health and Human Services, too, to search for relevant documents. NCI did issue a press statement (**Attachment 2**) on February 14, 1996, regarding the SEPTA campaign's representation of information from the scientific literature. A search of NCI's central files, and among files of queried NCI staff, revealed no correspondence since 1993 concerning other advertisements making other cancer claims.

9. In a line of questioning at the July 20 hearing before the Health and Environment Subcommittee, the NCI witness was asked about a very substantial body of research linking cancer to what is clearly an eminently avoidable exposure which you did not mention in your written testimony. Fully 25 out of 31 epidemiologic studies worldwide and 11 out of 12 studies in the United States (many of which, I am told, were conducted or funded by the NCI) show that women who elect to have even one induced abortion show an elevated risk of subsequent breast cancer. What studies has NCI conducted or funded related to the link between abortion and breast cancer?

*Note: The written testimony for the July 20 hearing focused on recent advances in cancer treatment, as it was our understanding that this was the intended topic of the hearing.

The body of research conducted before 1997 was, as described in a systematic review of the literature by respected epidemiologists, "inadequate to infer with confidence the relation between induced or spontaneous abortion and breast cancer risk, but it appears that any such relation is likely to be small or non-existent." Three points stood out in 1996. The first point was that the type of study (case-control interview study) that dominated the scientific literature at that time was subject to a demonstrated bias ("recall bias")[1] that tended to create an association where such association might not actually exist. Also, many of the early studies had no controls for other important risk factors. The second point was that the published studies showed no consistency in findings—and those that did showed what epidemiologists term "a weak association" (a relative risk between 0.7 and 1.3), or difficult to distinguish from bias or chance. The third point was that it seemed unlikely that the type of study that was needed—a study design unencumbered by recall bias, such as a cohort study—could be performed in the United States.

Epidemiologists thus regarded with interest the very large study, reported in 1997, which examined medical records—not personal interviews—from the entire female population of Denmark. In Denmark, routinely maintained population registries of births, deaths, medical procedures, and cancer make it possible to compile the data required on a large scale *without* recall bias and with great statistical precision. The study found no increased risk of breast cancer in the Danish women who had recorded abortions, as compared with women with no record of abortion.

The NCI conducts and funds many epidemiologic studies of breast cancer. Often included in the surveys and/or questionnaires are inquiries about a woman's reproductive history which, as stated above in the response to Question 2, is a strong determinant for breast cancer. These questions typically address her history of spontaneous abortion, induced abortion, or full term pregnancy. NCI has funded three studies directly related to abortion as a possible risk factor. They are listed below:

Breast Cancer in Relation to Prior Induced Abortion (completed 1990) (PI: Daling—Fred Hutchinson Cancer Research Center, Seattle)

Induced Abortion and Risk of Breast Cancer in Shanghai (completed 1997) (PI: Thomas—Fred Hutchinson Cancer Research Center, Seattle)

Induced Abortion and Breast Cancer Risk (expected completion 1999) (PI: De-Kun—Kaiser Foundation Research Institute, CA)

In summary, the scientific literature does not suggest that women who have even one abortion show elevated risk. It remains true that a woman whose first pregnancy is interrupted, either by spontaneous or induced abortion, does not gain the same degree of protection against breast cancer as the woman who is pregnant for the first time at the same age and carries her first pregnancy to term; instead, she has delayed her age at first birth. The biologic effect of abortion is seen by comparing two women who give birth for the first time at the same age, one of whom had a prior terminated pregnancy. These two women have the same subsequent risk of developing breast cancer, based on the epidemiologic data available today.

10. Research presented to the Committee shows that induced abortion has been linked with increased risk of breast cancer. What has NCI done to alert women that induced abortion has been consistently associated with increased breast cancer risk? How has NCI focused its public information on at-risk populations?

Experts at NCI and elsewhere find that the evidence suggests that induced abortion is not associated with an increased risk for breast cancer. Our information to women concerned about breast cancer risk after abortion addresses the research data to date, and includes discussions about data inconsistencies. We also emphasize the importance of a woman's discussing her personal risk of breast cancer with her physician.

In general, NCI reaches out to patients, their families, health care providers, researchers, and the public to bring them the most accurate, up-to-date cancer information. The NCI provides that information by telephone, on the Internet, through the media, in partnership with other organizations, and through a wealth of printed and audiovisual materials.

- The *Cancer Information Service* (CIS) answers about 500,000 calls a year at 19 regional offices. The toll-free number, *1-800-4-CANCER,* connects English- and Spanish-speaking callers with the office that serves their area. The CIS provides nationwide service to all 50 states and Puerto Rico. It also has an outreach program that develops partnerships with nonprofit, private, and other government agencies at national, regional, and local levels. Two-thirds of CIS partners focus on reaching minority populations.
- *PDQ* is NCI's computerized database that gives patients, health professionals, and the public quick and easy access to the latest treatment, supportive care, screening, and prevention information, as well as descriptions of clinical trials that are open for enrollment.

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[1] Women under-report abortions, yet breast cancer patients are more willing to acknowledge a previous abortion than other women—a difference that produces "recall bias."

- NCI's *Office of liaison Activities* works with national advocacy, voluntary, and professional organizations concerned about cancer to disseminate the latest, most accurate cancer information, and collaborates with these groups in areas of mutual interest. These organizations influence their members, the media, the public, and policymakers.
- NCI is developing a *publication on genetic testing* to help people decide if testing is right for them. NCI is also working to increase health care professional awareness and knowledge of human genetics and related ethical, legal, and psycho-social issues.
- NCI develops *media and print materials* designed for distribution to a variety of audiences. Some of these are designed specially for minorities and the medically underserved and are often implemented as part of national campaigns. These materials support the main message of a campaign (for example, women over age 40 should have regular mammograms) but are designed to be used by community leaders. For example, some materials for mammography screening include posters in English for African-American, Asian, and Native American women, and in Spanish, Vietnamese, Chinese and Korean. NCI also contributed to a nationally syndicated Spanish radio show promoting breast and cervical cancer prevention and detection.

11. I understand that the body of worldwide epidemiological research on the link between abortion and breast cancer reaches back as far as 1957. And the first such study conducted in the United States occurred as early as 1981. Is it not a fact that a majority of these studies show an increased risk (average about 30%) among women who have chosen abortion even just once?

The only cohort study published before 1996 found a statistically significant negative association (that is, abortion was associated with reduced risk for breast cancer). Of the 18 case-control studies published through 1996, most found no statistically significant association, positive or negative. Most of these studies did not control for known risk factors, or were limited by inadequate or possibly biased reporting of abortions. Because a very weak overall association might obscure a stronger one in a subgroup of women (perhaps young women), investigators also reported any associations noted in subgroups, even though the number of those subjects was very small. The subgroups noted to be at risk in one study were not found to be at risk in other studies. Thus, even before the large Danish cohort study was published the weight of evidence suggested no association, or a very weak one. There remains some uncertainty about the relative risk for women with very late induced abortions. More data on this finding would be valuable.

12. The NCI website on "Abortion and Breast Cancer" states that "although it has been the subject of extensive research, there is no convincing evidence of a direct relationship between breast cancer and either induced or spontaneous abortion. Available data are inconsistent and inconclusive, with some studies indicating small elevations in risk, and others showing no risk associated with either induced or spontaneous abortions."

A. Please identify and provide copies of the "extensive research" to which the website text refers. Was this research peer-reviewed?

I have attached copies of a systematic review of the literature published in 1996, a Dutch case-control study published later, and the large Danish cohort study (Attachments 3, 4, and 5). Each of these papers contain an extensive bibliography which, when taken as a whole, represent the body of literature used by NCI experts to develop the fact sheet to which you refer. All of these papers were published in peer-reviewed journals.

B. The website states that there is no "convincing evidence." What are NCI's criteria for identifying research that would be considered "convincing"? Are there statistical benchmarks that NCI uses to distinguish evidence that is convincing and that which is not? How is this evidence measured that would control for bias among researchers or program evaluators?

C. Does NCI draw a distinction between "direct relationship" and "indirect relationship" in determining causality?

D. NCI states that "available data are inconsistent and inconclusive." Are the data inconsistent, or are the studies inconsistent? What accounts for data that "are inconsistent and inconclusive"? Has NCI attempted to replicate studies that may have shown a link between breast cancer and induced abortion?

E. The NCI website states that some studies indicate a "small elevation in risk." What does "small elevation in risk" mean in this context? By saying there is a "small elevation in risk," is NCI placing the risk on a continuum between no risk and high risk? How does the "small elevation in risk" rank on a comparative risk analysis continuum? Based on this continuum, what action has NCI or other Federal agencies taken to warn consumers of cancer risk-factors that are comparable to that of induced abortion? Does "small elevation in risk" mean "acceptable risk"? How does NCI determine that something is an acceptably small risk?

Epidemiologists use the terms "weak associations" or "small risks" to express assessment of whether an association is "real"; that is, the probability that a factor causes the development of disease. Epidemiologic studies can be subject to errors of several types: biases in selection of study participants; biases in the observation of comparative data (such as the recall bias so problematic in collecting interview data on induced abortion); and statistical imprecision as the study size becomes smaller. Thus, "small" or "weak" are terms associated with the level of error methodologically expected for (1) chance occurrence, (2) a particular feature of the disease or the exposure, and (3) study design. The increased risk of developing breast cancer associated with each risk factor (see Question 2, above, for examples) varies from 1.5 to 4 times average risk.

An association typically is estimated as the ratio of risks, or the "relative risk." "Relative risk" is the ratio of disease incidence in the exposed population to the incidence in the unexposed population. A relative risk of "1.0" means that women exposed and women unexposed to a factor have the same risk of developing disease. It is a mathematical computation well-suited for assessing biologic connection. It is not intended to address comparison of absolute risk to benefit, or to judge what is acceptable risk to each individual. The NCI publishes widely the facts known about possible breast cancer risks, but decisions about "acceptable" risks must be made by a woman and her health care provider.

For the relationship between abortion and breast cancer, the most complete current summary of the uncertainty comes from the Danish population record study. The authors estimate that the relative risk for breast cancer in women with a recorded abortion is most likely between 0.94 and 1.06, with a very narrow interval of uncertainty because the study was very large. If a relative risk of "1.0" means that women exposed and women unexposed to a factor have the same risk, then the Danish population record study demonstrates that the women exposed to—and those not exposed to—the risk factor (induced abortion) have the same risk.

In many case control studies, a relative risk of 1.3 (or equivalently, a protective effect seen in a relative risk of 0.7) would be weak, small, or low. A relative risk of 2.0 is moderate. For example, if the initial research suggestion of an overall relative risk of 1.3 for developing breast cancer after abortion were supported by large and well-controlled epidemiologic studies, and otherwise fulfilled criteria for causality (see Question 12F. below), NCI would, as with other peer-reviewed information, make that available through all our mechanisms of information dissemination (see Question 10, above). NCI takes its responsibility for the public trust very seriously. All peer-reviewed study data are considered carefully, continuously, and comprehensively before we will say with certainty that a factor imparts a cancer risk. As discussed previously, the scientific literature to date does not suggest that women who have even one abortion show elevated risk. Our publications currently reflect this.

F. NCI also states that some studies indicate "no risk." What level of "elevation of risk" is considered to be "no risk" by NCI? How is "no risk" distinguished from that of "small risk" when proving causality is so difficult?

Evaluation of causality requires consideration of various types of evidence. Whether an exposure *causes* cancer may be assessed via several similar schema, the most common being the Bradford Hill criteria: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy. In many case control studies, a relative risk of 1.3 (or equivalently, a protective effect seen in a relative risk of 0.7) would be weak, small, or low. The authors of the Danish study estimate that the relative risk for breast cancer in women with a recorded abortion is most likely between 0.94 and 1.06, with a very narrow interval of uncertainty because the study was very large. This falls below the level of risk epidemiologists would consider weak, small, or low.

13. Is it true that epidemiologic research has found no overall link between spontaneous abortion and breast cancer? Is that not also consistent with the fact that most pregnancies which abort spontaneously are characterized by subnormal estrogen levels, whereas normal pregnancy levels of estrogen are several times higher than non-pregnant levels? Is it also true that some form of overexposure to estrogen, which stimulates the growth of both normal and precancerous breast tissue, is the mechanism by which most of the known breast cancer risk factors operate?

Yes, it is true that research has found no overall link between spontaneous abortion and breast cancer. There are many causes of spontaneous abortion, and not all of them are characterized by subnormal estrogen levels. Breast cancer is a cancer that is hormonally responsive, but it is unclear that estrogen is the only hormone involved. Other hormones may also play an important etiologic role.

14. The NCI website's first paragraph concludes with the sentence: "The scientific rationale for an association between abortion and breast cancer is based on limited experimental data in rats, and is not consistent with human data." Is this data to which you refer the Russo and Russo 1980 study? Is it accurate to summarize that this study, where rats were all given a chemical carcinogen, most of those rats which were allowed to bear offspring did not get breast cancer, while most of those which had their pregnancies surgically aborted did get breast cancer?

The data referred to in the NCI Fact Sheet on the Web site is the Russo & Russo study data. For breast cancer studies, suitable animal models have not been found, so extrapolating from animal data to the human model may not infer an absolute comparison. Russo & Russo found that pregnant rats who carried to term developed fewer mammary tumors than did rats who never were pregnant, or whose pregnancies were terminated.

15. The NCI website refers to studies finding "small elevations in risk" in the link between abortion and breast cancer. A 1994 Howard University study on African-American women here in the Washington, DC area showed a more than three-fold increase in breast cancer risk with induced abortion. That same study showed that the risk was almost five-fold for African-American women over 50 years old. Is it accurate to call that kind of risk elevation "small"?

Abortion was not a risk factor studied in the project referred to above. The risk you cite was actually the risk associated with a family history of breast cancer among women with two or more abortions. This was not the risk associated with abortion.

Please do not hesitate to contact me if you have further questions.

Sincerely,

RICHARD D. KLAUSNER
Director

Attachments

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HERPES SIMPLEX VIRUS TYPE 2 IN THE UNITED STATES, 1976 TO 1994

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ABSTRACT

Background Herpes simplex virus type 2 (HSV-2) infection is usually transmitted sexually and can cause recurrent, painful genital ulcers. In neonates the infection is potentially lethal. We investigated the seroprevalence and correlates of HSV-2 infection in the United States and identified changes in HSV-2 seroprevalence since the late 1970s.

Methods Serum samples and questionnaire data were collected during the National Health and Nutrition Examination Surveys (NHANES) II (1976 to 1980) and III (1988 to 1994). HSV-2 antibody was assessed with an immunodot assay specific for glycoprotein gG-2 of HSV-2.

Results From 1988 to 1994, the seroprevalence of HSV-2 in persons 12 years of age or older in the United States was 21.9 percent (95 percent confidence interval, 20.2 to 23.6 percent), corresponding to 45 million infected people in the noninstitutionalized civilian population. The seroprevalence was higher among women (25.6 percent) than men (17.8 percent) and higher among blacks (45.9 percent) than whites (17.6 percent). Less than 10 percent of all those who were seropositive reported a history of genital herpes infection. In a multivariate model, the independent predictors of HSV-2 seropositivity were female sex, black race or Mexican-American ethnic background, older age, less education, poverty, cocaine use, and a greater lifetime number of sexual partners. As compared with the period from 1976 to 1980, the age-adjusted seroprevalence of HSV-2 rose 30 percent (95 percent confidence interval, 15.8 to 45.8 percent). The seroprevalence quintupled among white teenagers and doubled among whites in their twenties. Among blacks and older whites, the increases were smaller.

Conclusions Since the late 1970s, the prevalence of HSV-2 infection has increased by 30 percent, and HSV-2 is now detectable in roughly one of five persons 12 years of age or older nationwide. Improvements in the prevention of HSV-2 infection are needed, particularly since genital ulcers may facilitate the transmission of the human immunodeficiency virus. (N Engl J Med 1997;337:1105-11.)

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HERPES simplex virus type 2 (HSV-2) causes vesicular and ulcerative lesions in adults[1-3] and may cause severe systemic disease in neonates and immunosuppressed hosts.[4-6] In addition, genital ulceration caused by HSV-2 may facilitate the transmission of the human immunodeficiency virus (HIV).[7-12] Infections with HSV-2 typically affect the genital area, and transmission is usually sexual.[6,13,14] In contrast, herpes simplex virus type 1 (HSV-1) commonly causes oropharyngeal infection, and transmission is primarily by nongenital personal contact.[2,15] However, both viruses are capable of causing either genital or oropharyngeal infection and can produce mucosal lesions that are clinically indistinguishable. After primary infection, herpes simplex viruses enter a latent state in the nerve ganglia and may emerge later to cause recurrent active infection.

Assessing the extent of HSV-2 infection nationwide is difficult, for several reasons. In most states, HSV-2 infection is not a reportable disease. Furthermore, most people with HSV-2 are unaware of the infection.[5,14,16-20] And, although the number of initial visits to physicians' offices for genital HSV infection increased from about 75,000 per year in 1978 to more than 150,000 per year in the early 1990s,[21] it is uncertain whether this increase was due to a real increase in incidence or to increased public awareness and improved diagnosis and treatment of genital herpes. For these reasons, serologic methods have

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been the best way to study the epidemiology of HSV-2. Comprehensive serologic data on HSV-2 in the United States were collected during the second National Health and Nutrition Examination Survey (NHANES II) between 1976 and 1980.[22]

We report here the results of a nationally representative serologic survey of HSV-2 that was done as part of NHANES III from 1988 to 1994. NHANES III had a larger sample than NHANES II and included information on behavioral risk factors for HSV-2 infection. In addition, the new survey allows us to see changes in HSV-2 seroprevalence over the 13 years between the midpoints of the two surveys. During this period, public awareness of genital herpes and other sexually transmitted diseases increased, and national programs to prevent HIV infection were begun.

METHODS

Study Populations and Sample Design

The NHANES program comprises a series of cross-sectional national surveys conducted by the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC). Each survey had a complex, stratified, multistage, probability-cluster design for selecting a sample representative of the noninstitutionalized civilian population of the United States.[22,24] The total sample was larger in NHANES III (40,000) than in NHANES II (28,000).

In NHANES III, children under 5 years of age, persons 60 years of age or older, Mexican Americans, and blacks were sampled at higher rates than other persons. Race or ethnic group was defined by self-report as non-Hispanic white or non-Hispanic black (referred to as "white" and "black" in this article), or as Mexican American. People who did not place themselves in any of these categories were classified as "other" and were included with the total population.

The poverty-index ratio in NHANES III was calculated by dividing the total family income by the poverty threshold, with adjustment for the family size in the year of the interview, as determined by the Bureau of the Census.[25] Residence in a county located in a metropolitan area was defined as urban residence. All other counties were defined as nonurban. Questions about the lifetime number of sexual partners, age at first intercourse, cocaine use, and history of genital herpes were asked of all study participants between 18 and 59 years old. Whether the participant had a history of genital herpes was addressed by the question, "Have you ever had genital herpes?"

In NHANES II, preschool children, older people, and people living below the poverty level were oversampled; the upper age limit was 74 years. Race was defined by self-report as "white," "black," or "other"; in that study, persons who gave their ancestry as "Hispanic" were classified as "other" so that the results could be compared with those of NHANES III.

Responses to the Surveys

Of the persons originally selected for NHANES III, 82.5 percent were interviewed, and HSV-2 test results were available for 60.2 percent. The reasons that results were unavailable included the inability to locate the selected subject, refusal by that person to be interviewed or to have blood drawn, unsuccessful venipuncture, the need to use serum for other tests, and the loss of serum samples during transportation, storage, or processing. The percentages of selected persons who agreed to be interviewed and the percentages of those for whom HSV-2 test results were available were similar among persons of different sex, race or ethnic group, and age, except that HSV-2 test results were less likely to be available for persons 70 years old or older (51.9 percent).

The rates of college attendance, rates of use of cocaine, and lifetime numbers of sex partners were similar among interviewed persons for whom HSV-2 results were available and those for whom the results were unavailable. The results were more likely to be available for persons living below the poverty level (71.9 percent) than for those living at or above the poverty level (58.1 percent).

An analysis of survey nonresponse in NHANES II has been published elsewhere.[26] Nonresponse to the survey did not appear to introduce bias into the overall results.

Serologic Testing

Serum samples in both NHANES II and NHANES III were tested for antibodies to HSV-2 with the same type-specific immunodot test, performed in the same laboratory.[22,27,28] The purified glycoprotein gG-2 of HSV-2, which is specific for HSV-2, served as antigen in the assay. The sensitivity of the immunodot test for recurrent, culture-proved genital HSV-2 infection is over 98 percent, and the specificity is over 99 percent.[27] The quality of the HSV-2 testing was confirmed during both surveys by testing, with each reaction plate, positive and negative controls derived from pools of reference serum.

In NHANES III, all the available serum samples from persons 12 years of age or older were tested for type-specific HSV-2 antibody. In NHANES II, a subgroup of serum samples was tested for HSV-2, as described previously.[22] Subgroup sampling weights were calculated to account for the sampling design and for the unavailability of serum samples according to sex, race or ethnic group, and age group. The final weight for each person in the sample in NHANES II was calculated as the product of the overall survey weight and the subgroup sampling weight.

As previously described,[22] in NHANES II serum samples were first screened with a non–type-specific enzyme-linked immunosorbent assay, which detected any antibodies to HSV-1 or HSV-2.[27,28] Serum samples that were positive on the non–type-specific screening test were subsequently tested with the type-specific test. Serum samples that were negative on the screening test were then presumptively assigned a negative test result for the type-specific immunodot test, thus limiting the use of the scarce type-specific testing reagent. To ensure that the screening test had a negligible effect on the overall sensitivity or specificity of HSV-2 testing, 245 serum samples from a health maintenance organization that were negative on the screening test were tested with the type-specific test; no type-specific HSV-2 antibody was detected in any of the samples.[27]

Statistical Analysis

For both surveys, the prevalence estimates were weighted to represent the total U.S. population and to account for oversampling and nonresponse to the household interview and physical examination. The weights were further ratio-adjusted according to age, sex, and race or ethnic group to estimates of the noninstitutionalized civilian U.S. population taken from the Current Population Survey, adjusted for undercounting.[29,30] Standard errors were calculated with SUDAAN.[31] The approximate standard errors of prevalence ratios were calculated by the delta method.[32] For comparisons between NHANES II and III and across population subgroups of NHANES III, the data were age-adjusted to the 1980 U.S. population by the direct method,[33] and nonoverlapping 95 percent confidence intervals were taken to indicate statistically significant changes in seroprevalence.

Logistic regression was used to identify predictors of HSV-2 infection. The initial model included demographic and behavioral variables that had univariate odds ratios with 95 percent confidence intervals excluding 1.0. By using stepwise backward elimination, variables with P values greater than 0.05 were then removed from the model.

RESULTS

NHANES III (1988 to 1994)

The seroprevalence of HSV-2 among study participants 12 years of age or older was 21.9 percent (95 percent confidence interval, 20.2 to 23.6 percent) (Table 1). This prevalence corresponds to 45 million infected people in the noninstitutionalized civilian U.S. population. The seroprevalence was higher among women (25.6 percent) than among men (17.8 percent), yielding a female:male prevalence ratio of 1.4 (95 percent confidence interval, 1.2 to 1.7). The seroprevalence was 17.6 percent among whites, 45.9 percent among blacks, and 22.3 percent among Mexican Americans, yielding a black:white prevalence ratio of 2.6 (95 percent confidence interval, 2.3 to 2.9) and a Mexican-American:white prevalence ratio of 1.3 (95 percent confidence interval, 1.1 to 1.4). The female:male prevalence ratios were similar for each race or ethnic group. With increasing age, the overall HSV-2 seroprevalence rose rapidly in the younger age groups and then remained stable among people older than 30 years, in the range of 24 percent to 28 percent.

By univariate analysis, HSV-2 seroprevalence was associated with a number of variables (Table 2). HSV-2 seroprevalence was higher among persons who were divorced or separated and those who were widowed than among single or married people, those with less education, and those living below the poverty level. There was no statistically significant difference in HSV-2 seroprevalence between urban and nonurban areas, and only a slight variation among the four regions of the United States. As far as behavioral variables were concerned, HSV-2 seroprevalence was higher among those who had ever used cocaine, those who had first had intercourse at the age of 17 or younger, and those with a greater lifetime number of sexual partners.

With increasing lifetime numbers of sexual partners, HSV-2 seroprevalence initially rose more sharply for blacks than for whites, even after adjustment for age (Fig. 1). For example, the age-adjusted seroprevalence among blacks who reported having one partner over a lifetime was 4.4 times that among whites reporting one partner; this held true both for men and women. By contrast, with increasing lifetime numbers of sexual partners, the seroprevalence among blacks leveled off, whereas it increased sharply among whites.

Only 2.6 percent of adults report ever having had genital herpes. Persons with a history of genital herpes had an HSV-2 seroprevalence of 81.5 percent, whereas all other persons had a seroprevalence of 21.6 percent (Table 2). The sensitivity of a self-reported history of genital herpes for the presence of HSV-2 antibody was 9.2 percent overall and was similar for both sexes. In contrast, the sensitivity of a self-reported history of genital herpes for the presence of HSV-2 antibody differed markedly according to race or ethnic group; it was 12.2 percent for whites, 3.7 percent for blacks, and 3.8 percent for Mexican Americans.

In a multivariate model that examined the demographic and behavioral variables associated with HSV-2 status on univariate analysis, differences associated with marital status and age at first sexual intercourse were found not to be statistically significant ($P>0.05$) and were therefore dropped from the model. In the model, the multivariate independent

TABLE 1. HSV-2 SEROPREVALENCE IN NHANES III (1988 TO 1994) ACCORDING TO SEX, AGE, AND RACE OR ETHNIC GROUP.*

VARIABLE	OVERALL†		WHITES		BLACKS		MEXICAN AMERICANS	
	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)	SAMPLE SIZE	PERCENT PREVALENCE (95% CI)
Sex								
Both sexes	13,094	21.9 (20.2–23.6)	4727	17.6 (15.7–19.5)	3884	45.9 (43.9–47.9)	3991	22.3 (21.2–23.5)
Male	6,407	17.8 (15.6–20.2)	2383	14.9 (12.3–18.1)	1798	34.7 (32.5–37.0)	1992	19.2 (17.9–20.6)
Female	6,687	25.6 (24.0–27.3)	2344	20.2 (18.3–22.2)	2086	55.1 (52.7–57.5)	1999	25.7 (24.2–27.2)
Age (yr)								
12–19	2,396	5.6 (4.3–7.2)	605	4.5 (3.0–6.8)	806	8.7 (6.4–11.9)	870	5.4 (4.0–7.3)
20–29	2,750	17.2 (15.0–19.7)	675	14.7 (12.0–18.1)	891	33.6 (30.3–37.2)	1072	14.8 (12.6–17.5)
30–39	2,567	27.8 (24.8–31.2)	792	21.9 (18.7–25.6)	884	54.4 (50.5–58.6)	793	28.7 (26.3–31.4)
40–49	2,061	26.6 (23.5–30.0)	724	19.9 (16.4–24.1)	634	58.9 (55.7–62.4)	612	33.0 (28.4–38.3)
50–59	884	25.1 (21.5–29.4)	456	19.4 (15.6–24.1)	211	62.7 (54.4–72.3)	185	42.5 (31.6–57.1)
60–69	1,069	24.3 (20.2–29.1)	480	18.2 (13.7–24.0)	258	76.8 (72.3–81.5)	310	38.7 (32.0–46.8)
≥70	1,367	27.7 (24.6–31.1)	995	23.3 (20.0–27.0)	200	74.3 (67.6–81.8)	149	44.6 (38.8–51.3)

*CI denotes confidence interval.

†Totals differ from the sums for whites, blacks, and Mexican Americans because other races and ethnic groups are included in the overall totals.

Table 2. HSV-2 Seroprevalence in NHANES III (1988 to 1994) According to Demographic and Behavioral Factors and History of Herpes.*

Variable	Sample Size†	Percent Prevalence (95% CI)
Demographic factors		
Marital status		
Single	2793	17.1 (14.9–19.8)
Married	6732	21.5 (19.3–23.9)
Divorced or separated	1222	39.0 (34.9–43.7)
Widowed	813	35.0 (30.1–40.6)
Education (last year completed)		
Elementary	2194	35.2 (30.3–40.9)
High school	5775	24.2 (22.6–25.9)
Some college	3539	19.2 (16.8–22.0)
Poverty index		
Below poverty level	2848	33.5 (30.6–36.7)
At or above poverty level	8731	21.3 (19.3–23.4)
Residence		
Urban	9472	23.3 (21.3–25.5)
Nonurban	2107	21.0 (17.8–24.6)
Region		
Northeast	1488	21.7 (16.8–27.9)
Midwest	2070	18.4 (15.4–21.9)
South	5323	24.8 (22.4–27.5)
West	2698	26.4 (23.8–29.3)
Behavioral factors		
Ever used cocaine		
Yes	1011	33.9 (29.2–39.4)
No	7860	20.6 (18.9–22.4)
Age at first sexual intercourse (yr)		
≤17	5055	26.8 (24.7–29.1)
≥18	3437	18.9 (16.6–21.6)
Lifetime number of sexual partners		
0	361	3.0 (1.3–7.0)
1	1807	10.2 (8.2–12.7)
2–4	2633	20.7 (18.2–23.6)
5–9	1716	25.9 (22.7–29.5)
10–49	1830	30.9 (27.5–34.6)
≥50	346	46.1 (39.5–53.9)
Answer to question: "Have you ever had genital herpes?"		
Yes	167	81.5 (70.0–94.9)
No	8302	21.6 (19.8–23.5)

*The age ranges are ≥17 years for demographic variables and 18 to 59 for behavioral variables. CI denotes confidence interval.

†In some cases, data were not available for all subjects.

predictors of HSV-2 serologic status were female sex, black race or Mexican-American ethnic background, older age, less formal education, an income below the poverty level, a greater lifetime number of sexual partners, and having ever used cocaine. The strongest predictors (with odds ratios greater than 3.0) were sex, race or ethnic group, age, and the lifetime number of sexual partners.

Trends in HSV-2 Seroprevalence between NHANES II (1976 to 1980) and NHANES III (1988 to 1994)

The age-adjusted overall prevalence of HSV-2 antibody rose from 16.0 percent in NHANES II to 20.8 percent in NHANES III (Table 3), a relative increase of 30 percent (95 percent confidence interval, 15.8 to 45.8 percent). The relative increases among men and women were similar. Among both whites and blacks there were similar absolute increases, but the relative increases were greater among whites because of the lower base-line prevalence among whites. The age-adjusted HSV-2 seroprevalence among whites increased from 12.7 percent in NHANES II to 16.5 percent in NHANES III, a relative increase of 30 percent (95 percent confidence interval, 9.9 to 54.3 percent). Among blacks, the age-adjusted seroprevalence increased from 43.6 to 47.6 percent, a relative increase of 9 percent (95 percent confidence interval, −1.2 to 20.4 percent).

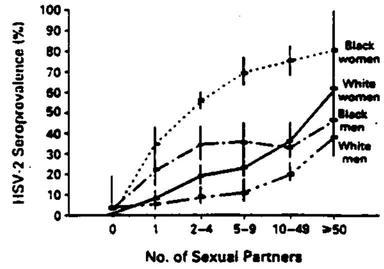

Figure 1. HSV-2 Seroprevalence According to the Lifetime Number of Sexual Partners, Adjusted for Age, for Black and White Men and Women in NHANES III (1988 to 1994).

Bars indicate 95 percent confidence intervals.

The increases in HSV-2 seroprevalence between NHANES II and NHANES III were concentrated in the younger age groups. There were statistically significant increases overall in the three youngest age groups, encompassing subjects from 12 to 39 years of age (Fig. 2). Among whites, the seroprevalence increased from 0.96 to 4.5 percent (prevalence ratio, 4.7; 95 percent confidence interval, 1.4 to 16.0) among 12-to-19-year-olds, and from 7.7 to 14.7 percent (prevalence ratio, 1.9; 95 percent confidence interval, 1.3 to 2.8) among 20-to-29-year-olds. Among older whites and among blacks, the increases were smaller and did not reach statistical significance in any age group.

DISCUSSION

These findings document the increasing seroprevalence of HSV-2 in the United States during an era in which the acquired immunodeficiency syndrome (AIDS) became recognized and national prevention efforts were initiated. During the period covered by NHANES III (1988 to 1994), the overall seroprevalence of HSV-2 in the United States was 21.9 percent. From NHANES II (1976 to 1980) to NHANES III,

TABLE 3. CHANGES IN AGE-ADJUSTED HSV-2 SEROPREVALENCE BETWEEN NHANES II (1976 TO 1980) AND NHANES III (1988 TO 1994).*

CATEGORY OF SUBJECTS	NHANES II		NHANES III		PERCENT RELATIVE INCREASE
	SAMPLE SIZE	AGE-ADJUSTED PERCENT SEROPREVALENCE (95% CI)	SAMPLE SIZE	AGE-ADJUSTED PERCENT SEROPREVALENCE (95% CI)	
All races and ethnic groups†					
Both sexes	3597	16.0 (14.7–17.4)	13,094	20.8 (19.2–22.5)	30
Men	1681	13.4 (11.7–15.4)	6,407	17.1 (15.0–19.5)	27
Women	1916	18.4 (16.5–20.5)	6,687	24.2 (22.7–25.7)	32
Whites					
Both sexes	2153	12.7 (11.2–14.3)	4,727	16.5 (14.7–18.5)	30
Men	1021	10.7 (8.7–13.0)	2,383	14.1 (11.6–17.2)	32
Women	1132	14.5 (12.4–17.0)	2,344	18.7 (17.0–20.5)	29
Blacks					
Both sexes	1130	43.6 (40.0–47.6)	3,384	47.6 (45.4–49.9)	9
Men	495	34.1 (30.0–38.7)	1,798	37.5 (34.8–40.3)	10
Women	635	51.4 (47.6–55.6)	2,086	55.7 (53.3–58.2)	8

*Seroprevalence has been age-adjusted to the 1980 census. The age range is ≥12 years. CI denotes confidence interval.

†Totals differ from the numbers for whites and blacks because other races and ethnic groups are included in the category of all races and ethnic groups.

the age-adjusted seroprevalence increased by 30 percent, with the greatest relative increases among young whites.

Women were about 45 percent more likely than men to be infected with HSV-2 during both study periods. Potential explanations for this finding include the higher efficiency of HSV-2 transmission from men to women as compared with that from women to men[14] and differences between women and men in sexual behavior.[34-36] For example, women are more likely than men to choose sexual partners who are older than themselves[36] and who therefore have an increased risk of HSV-2 infection.

In both surveys, blacks were more likely than other racial or ethnic groups to be infected with HSV-2. The disparities may be due to a variety of factors, both current and historical, which include racial and ethnic differences in the prevalence of poverty and low socioeconomic status, access to health care, sexual behavior, health-related behavior, and illicit drug use, as well as the age and sex composition of the population.[37-39]

Of the other demographic and behavioral factors assessed in NHANES III, the most strongly predictive of HSV-2 infection was the lifetime number of sexual partners. However, this effect was not the same for both sexes or for all races or ethnic groups (Fig. 1). In fact, black men and women who reported having had only one sexual partner over their lifetimes were more than four times as likely to be infected with HSV-2 as white men and women with one sexual partner. This observation is consistent with the idea that the pool of potential sexual partners is different for whites and blacks. Since white and black populations have different levels of HSV-2 prevalence and since sexual partnerships tend to form between members of the same race or ethnic group,[36,40] whites and blacks will typically face different risks of exposure to HSV-2 with each sexual partner. A similar difference has been observed between white and black women with respect to the risk of pelvic inflammatory disease.[41]

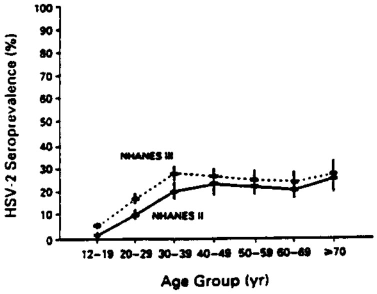

Figure 2. HSV-2 Seroprevalence According to Age in NHANES II (1976 to 1980) and NHANES III (1988 to 1994).

Bars indicate 95 percent confidence intervals.

The great majority of people with serologic evidence of HSV-2 infection in the current study had no history of genital herpes. However, previous studies have demonstrated that many or most seropositive persons shed HSV-2 that is detectable by culture from the genital tract,[5,17-19] and many have symptoms, such as itching and discharge, that are directly referable to HSV-2 detectable by culture. Such symptoms, however, are not often recognized as indicating an infection.[16,19]

Could the increases in HSV-2 seroprevalence among young people in the 13 years between the two surveys be related to changes in sexual behavior? During these years, AIDS was recognized as a public health problem, and large-scale HIV prevention efforts were initiated that might conceivably also have contributed to a reduction in HSV-2 infection. For example, condom use by young men more than doubled between 1979 and 1988.[42] Condoms are effective in preventing HIV transmission when they are properly used during every sexual encounter.[43] However, their effectiveness against HSV-2 transmission has been less well documented and may be more limited, because HSV-2 lesions can occur on areas of the body not covered by condoms.[43-45] On the other hand, despite AIDS-prevention efforts, the prevalence of premarital sexual experience and multiple sexual partners increased among both young whites and young blacks.[42,46-48] The increases in some types of risky behavior were more marked among whites.[46]

These results highlight the ongoing need to prevent HSV-2 and other sexually transmitted infections. A concerted national effort is needed to overcome barriers to the adoption of healthful sexual behavior, as emphasized in a recent report on sexually transmitted diseases from the Institute of Medicine.[49] In addition, improvements in the diagnosis and treatment of established HSV-2 infection may have some effect on the transmission of HSV-2, since suppressive therapy with antiviral medications has been shown to decrease viral shedding.[50-52] Finally, new preventive techniques, such as the use of HSV-2 vaccines[53-57] and topical microbicides[58] now under development, are urgently needed.

A primary goal of efforts to reduce HSV-2 infection should be the prevention of new HIV infections, since genital ulcers caused by HSV-2 may independently facilitate HIV transmission.[7-12] In the meantime, HSV-2 seroprevalence, as measured by NHANES, provides reliable data on the prevalence of this sexually transmitted disease in the United States. It may therefore be an important indicator to follow as we attempt to promote healthful sexual behavior and prevent sexually transmitted diseases, including HIV infection.

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Editorials

HERPES SIMPLEX VIRUS TYPE 2 — A PERSISTENT PROBLEM

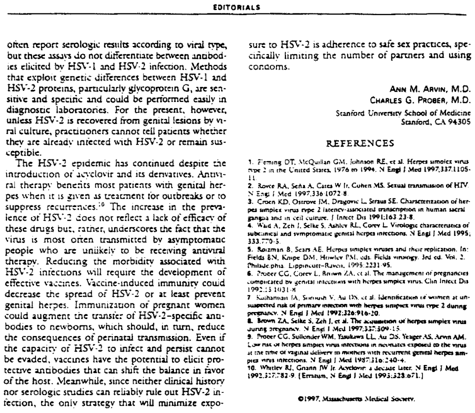
IN this issue of the *Journal*, Fleming and colleagues report that the age-adjusted seroprevalence of herpes simplex virus type 2 (HSV-2) in the United States is now 20.8 percent, an increase of approximately 30 percent over the 13 years between the second and third National Health and Nutrition Examination Surveys (NHANES II and III).[1] The obvious inference from the increase in HSV-2 infections is that the spread of sexually transmitted diseases continues unabated, despite the substantial educational efforts made in response to the epidemic of the human immunodeficiency virus (HIV). In NHANES III, HSV-2 seropositivity correlated with a higher lifetime number of sexual partners and with cocaine use, both of which are behavioral risk factors that are also associated with the acquisition of HIV.[2] A new concern about HSV-2 infection is that symptomatic genital herpes may facilitate the spread of HIV. When HSV-2 causes genital lesions, mucocutaneous barriers are disrupted and CD4+ T cells move to the site, thus making the transfer of HIV from an infected person more likely.

Understanding the epidemiology of HSV-2 requires knowing that most HSV-2 infections do not cause the classic ulcerative lesions that are easily recognized as genital herpes. Instead, most HSV-2 infections are asymptomatic, as confirmed by data from interviews of seropositive people in NHANES III. After inoculation and limited replication at genital sites, HSV-2 ascends along neuronal axons to establish latent infection in the lumbosacral sensory ganglia.[3] During this initial phase, infectious virus is present at genital sites for days or weeks, usually without lesions.[4] When a new cycle of viral replication is triggered, reactivation occurs and infectious virus is delivered back down the neural pathways to the mucosa or skin.[5] The return of infectious virus to genital sites during HSV-2 reactivation rarely causes any symptoms. HSV-2 is a chronic, persistent infection that, on any given day, causes subclinical reactivation in about 1 percent of infected persons.[6] Since about 45 million people in this country are now infected, HSV-2 can spread efficiently and silently through the population. People who have sexual contact with many partners will frequently have exposure to an infected person who is shedding HSV-2. As the overall prevalence of HSV-2 infection continues to rise, contact with fewer partners will permit exposure.

The most dramatic increase in the prevalence of HSV-2 infection observed by Fleming et al. was in the youngest age cohorts. Seroprevalence rose in all the groups studied, but it quintupled among white teenagers and doubled among whites in their 20s. The increases in HSV-2 infection in the younger cohorts means that a substantial number of women entering their childbearing years are infected with HSV-2 or are at risk of contracting infection because their partners are more likely to be infected. We found in 1992 that 9.5 percent of pregnant women were at risk of acquiring HSV-2 from an infected partner.[7] Again, exposure was often unsuspected because more than half the infected partners had no history of genital herpes. Brown et al. reported in a recent issue of the *Journal* that about 1 percent of a large cohort of previously uninfected pregnant women acquired HSV-2 during pregnancy.[8] There were no adverse consequences among the women with documented primary infections who had antibodies by the time of delivery. However, two of the seven infants of HSV-2–infected mothers who were born before maternal seroconversion and who were delivered vaginally became infected. By contrast, fewer than 2 percent of newborns whose mothers have reactivation of HSV-2 contract the disease.[9] These observations confirm the high risk of transmission associated with new maternal infections in late gestation and the efficacy of HSV type-specific antibodies in preventing neonatal herpes. The increasing rate of acquisition of HSV-2 infection among young adults increases the likelihood that infants will be exposed to HSV-2 at delivery. Despite antiviral therapy, neonatal herpes is still a life-threatening infection.[10]

Serologic assays that distinguish between antibodies to HSV-1 and antibodies to HSV-2 have refined our basic understanding of HSV-2 infection and the patterns of its transmission, but there is a lag in the transfer of this information to health care practitioners and the public. Since at least one in five people now has HSV-2 infection, those who have unprotected contact with multiple sexual partners should know that unsuspected exposure to HSV is virtually guaranteed. Patients who develop genital ulcers due to HSV-2 should understand that their illness is more likely to represent the reactivation of a previously unrecognized HSV-2 infection than a new infection traceable to a recent sexual partner. Even when the infection is new, it is quite plausible for the infecting partner to report no history or current symptoms of genital herpes. Understanding the biology of HSV-2 can help reduce mistaken accusations of infidelity. Silent spread is the rule for HSV-2, not the exception.

Diagnostic methods that are helpful for the clinical management of HSV-2 infection are limited. Type-specific assays for HSV antibodies are not yet available for clinical use. Commercial laboratories



often report serologic results according to viral type, but these assays do not differentiate between antibodies elicited by HSV-1 and HSV-2 infection. Methods that exploit genetic differences between HSV-1 and HSV-2 proteins, particularly glycoprotein G, are sensitive and specific and could be performed easily in diagnostic laboratories. For the present, however, unless HSV-2 is recovered from genital lesions by viral culture, practitioners cannot tell patients whether they are already infected with HSV-2 or remain susceptible.

The HSV-2 epidemic has continued despite the introduction of acyclovir and its derivatives. Antiviral therapy benefits most patients with genital herpes when it is given as treatment for outbreaks or to suppress recurrences.[10] The increase in the prevalence of HSV-2 does not reflect a lack of efficacy of these drugs but, rather, underscores the fact that the virus is most often transmitted by asymptomatic people who are unlikely to be receiving antiviral therapy. Reducing the morbidity associated with HSV-2 infections will require the development of effective vaccines. Vaccine-induced immunity could decrease the spread of HSV-2 or at least prevent genital herpes. Immunization of pregnant women could augment the transfer of HSV-2–specific antibodies to newborns, which should, in turn, reduce the consequences of perinatal transmission. Even if the capacity of HSV-2 to infect and persist cannot be evaded, vaccines have the potential to elicit protective antibodies that can shift the balance in favor of the host. Meanwhile, since neither clinical history nor serologic studies can reliably rule out HSV-2 infection, the only strategy that will minimize exposure to HSV-2 is adherence to safe sex practices, specifically limiting the number of partners and using condoms.

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Mr. COBURN. I would make one clarifying point. So it is important to people that are not medical here. There are non-aggressive forms of human papilloma virus; those are of no interest to us, because they have no effect. It is only those that are aggressive that we are concerned with, and it is only those that cause cancer. So that, when we discuss them in total, we diminish the importance of the aggressiveness of those that do affect humans, and it is important for everybody, when we are asking a question about HPV, we are talking about those that are carcinogenic or oncogenic, rather than those that aren't.

The other point that I would make, and I think our panel made, that is not the only cancer that they cause. We see cancer of the vulva, cancer of the rectum, cancer of the larynx associated with these same HPV subtypes.

And I would yield to the gentlelady from California.

Ms. ESHOO. Thank you for recognizing me, and I want to thank each one of the witnesses that are here today because you have given us highly informative testimony. I hope there are a lot of people that are tuned in or will hear this through a repeat program, wherever they are in this country, because I think in listening, that at least part the intent of this hearing is to educate. Educate, educate, educate.

The first request that I have, before I ask my question, is, Dr. Lee, Dr. Valdiserri, could you from the CDC provide for me—and perhaps the rest of the members of the subcommittee would like this as well—I would love to have a list of who you contract within my congressional district for the services that you provide. I was deeply involved in those issues before I came to the House, and the county board of supervisors, and established a whole network of clinics in a major county in the Bay area. So I would like to know who you are working with. Also, we should all be looking into whether we can do public service announcements in our congressional districts on this. Because to the extent that we get this out, and to the extent that we have something in place right now, and to the extent that this subcommittee and full committee and the Congress pass Mr. Lazio's and Congresswoman Capps' and my original co-sponsorship of the legislation, we can really go after this and be effective. So if you can do that, we would really appreciate it.

[The information referred to follows:]

Question. List of recipients (CBOs, etc) of BCCEDP funds in Ms. Eshoo's District (14th District in CA—includes Palo Alto)

Answer. CDC funds the California Breast and Cervical Cancer Early Detection Program (CBCCEDP) to:

- provide screening to medically underserved women for breast and cervical cancer
- provide appropriate and timely diagnostic evaluations for women with abnormal screening tests and treatment services if needed
- develop and disseminate public information and education related to the detection and control of breast and cervical cancer
- improve training of health professionals in the detection of these cancers
- and finally, evaluate program activities through the establishment of surveillance systems.

The CBCCEDP partners with many organizations throughout the State to provide specific services for at risk women. One such partnership in the 14th District of California is the Santa Clara Valley Center in San Jose, which has breast and cervical cancer screening providers located in Palo Alto. Women of the 14th District may also choose to receive services from the CBCCEDP sites of Alameda County Medical Center and San Francisco Department of Public Health.

Santa Clara Valley Center
P.O. Box 21949
San Jose, CA 95151-1940
Attn: Jennifer Sedbrook, (408) 289-9260

Alameda County Medical Center Fairmont Hospital Administration
15400 Foothill Boulevard
San Leandro, CA 94578
Attn: Carol Oakley, (510) 667-7848

San Francisco Department of Public Health
101 Grove Street, Room 321
San Francisco, CA 95151-1940
Attn: Diane Carr (415) 554-2878

Question. The National Breast and Cervical Cancer Early Detection Program's legislation (Public Law 101-354) provides states with funds to offer screening services to women of low-income. What mechanisms are in place to provide treatment to women who need it?

Answer. Ensuring that all women with abnormal screening results receive adequate follow-up and a definitive diagnosis is a crucial component of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). Thus, diagnostic services funded through the program include diagnostic mammography, breast ultrasound, breast biopsy fine needle aspiration, colposcopy, colposcopy-directed biopsy and endocervical curettage.

The legislation that authorizes the NBCCEDP does not allow resources appropriated for the program to be used for treatment. However, participating health agencies are required to identify and secure resources for diagnostic follow-up services that the program does not cover and for cancer treatment services for women in need, regardless of their ability to pay. CDC provides careful oversight to assure that women who need treatment receive it.

Analysis of program data for all abnormal screening mammograms reveals a median of 36 days between the initial screening mammogram and final diagnosis, and a median of 9 days between diagnosis of breast cancer and treatment. Additionally, surveillance data show that 96 percent of the women diagnosed with invasive or in situ breast cancer have initiated treatment. Of the remaining 4 percent, 2 percent reportedly refused care, 1 percent had a provider recommendation that treatment was not currently indicated, and 1 percent were lost to follow-up.

In addition, CDC contracted with Battelle Centers for Public Health Research and Evaluation and the University of Michigan to document the range of systems and strategies used by states to obtain resources for treatment and ensure that women diagnosed with cancer or precancerous lesions receive timely and appropriate follow-up and treatment services. Seven state programs (California, Michigan, Minnesota, New Mexico, New York, North Carolina, and Texas) were studied in depth, ending in December 1997. Almost 200 people were interviewed; more than half of them were screening, diagnostic service, and/or treatment providers in local communities.

The study results show that innovative and creative approaches have been implemented to identify and secure resources for follow-up and treatment services. Women diagnosed with cancer through the NBCCEDP are receiving treatment. Without exception, study respondents reported that of their clients diagnosed with breast cancer or invasive cervical cancer, all women who have wanted treatment have indeed initiated cancer therapy.

Creative partnerships and responses to the lack of NBCCEDP resources for some diagnostic services and all treatment services have been developed in programs at the state, local, and provider levels. Implemented strategies are very similar for breast and cervical cancer, although funding from state legislatures and private foundations is more prevalent for breast diagnostic services than for cervical diagnostic services or for cancer treatment in general. Additionally, each of the seven states studied currently has some type of fund, centralized at the state level, that supplements the services provided by the NBCCEDP. Many financial barriers to diagnostic follow-up and some for cancer treatment have been reduced.

Findings suggest that state programs and their partners have invested significant amounts of time and effort to develop systems of care for diagnostic follow-up and treatment, and that these systems appear to be working. Tremendous effort is involved in developing, implementing, and maintaining strategies and systems for these services. Rarely is there a standardized or set way that a state or even a facility uses to obtain services women need that are not covered by the NBCCEDP. Efforts typically are tailored to an individual client's needs and resources.

The goal of the NBCCEDP is to reduce mortality from breast and cervical cancers, and the success of this effort hinges on the identification and treatment of early stage cancers. As they have in the past, CDC and its state partners in the NBCCEDP will continue to give priority to this critical aspect of the early detection effort.

STRATEGIES FOR PROVIDING FOLLOW-UP AND TREATMENT SERVICES IN THE NATIONAL BREAST AND CERVICAL CANCER EARLY DETECTION PROGRAM UNITED STATES, 1997

The Breast and Cervical Cancer Mortality Prevention Act of 1990 (Public Law 101-354) authorized CDC to establish the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) to increase screening services for women at low income levels who are uninsured or underinsured (1). Although the NBCCEDP covers most diagnostic services that women need after receiving an abnormal mammography or Papanicolaou (Pap) test result, the program does not reimburse for breast biopsies. In addition, the Act prohibits the use of NBCCEDP funds for cancer treatment. Participating health agencies must ensure that NBCCEDP clients receive timely, appropriate diagnostic and treatment services. In 1996, CDC began a case study to determine how early detection programs in seven participating states (California, Michigan, Minnesota, New Mexico, New York, North Carolina, and Texas) identified resources and obtained diagnostic and treatment services. This report summarizes the results of the study (2), which indicate that respondents in these states reported that treatment had been initiated for almost all NBCCEDP clients in whom cancer was diagnosed. However, respondents also considered the strategies used to obtain these services as short-term solutions that were labor-intensive and diverted resources away from screening activities.

In the seven states, NBCCEDP sponsored screening services had been provided for ≥3 years, and breast cancer had been diagnosed in ≥60 women. The states were selected to provide a range of geographic locations, a combination of urban and rural populations, and racial/ethnic diversity among program clients. Researchers conducted semistructured interviews with 192 persons affiliated with the seven state programs. Of these interviewees, 120 (63%) were providers of screening, diagnostic, and/or treatment services; 58 (30%) were state program staff; and 14 (7%) were coalition members. Interviews included topics such as guidelines related to diagnostic and treatment services, strategies used to obtain and pay for services, level of effort required to secure these services, and changes in strategies over time. Each interview was tape recorded and transcribed. Using a systematic scheme derived from the research questions, three researchers coded the same transcripts until an interrater agreement of 80% was reached. Thereafter, all transcripts were coded independently. Coding results were entered into text analysis software that sorts text from transcripts into sets of information, themes, and evidence relevant to the specific research questions (3). The results reflect a synthesis of the interviewees' responses. Respondents described several strategies used to ensure necessary diagnostic and treatment services for women screened through the NBCCEDP. State level strategies in all states included 1) computerized tracking and follow-up systems that used program surveillance data to identify and manage clients in need of diagnostic and treatment services; 2) provisions in contracts requiring screening providers to arrange for diagnostic follow-up and treatment before screening women; and 3) arrangements with provider groups and state professional associations for free or reduced cost services for NBCCEDP clients. All states also had access to public or private funds to help support services not covered by the program; such revenue sources included state appropriations from general or tobacco tax revenues or funds from private foundations. These funds were available primarily for breast diagnostic services.

Local strategies tailored to the needs of individual clients were used to obtain diagnostic and treatment services. Common strategies reported by respondents included the following: providers billed public or private insurance plans; providers or local health departments helped clients apply for public assistance programs; providers referred clients to public hospitals; county indigent care funds and hospital community benefit programs financed services; clients received services through individually negotiated payment plans; and clients paid reduced or full fees for services.

Respondents strongly supported the continued growth of NBCCEDP and its goals but expressed several concerns. First, considerable time and effort were involved in developing and maintaining systems for diagnostic follow-up and treatment. Second, the process of identifying available resources within states for diagnostic and treatment services was considered labor-intensive. Third, the lack of coverage for diagnostic and treatment services negatively affected recruitment of providers and restricted the number of women screened. Fourth, respondents believed that an increasing number of physicians will not have the autonomy, because of changes in the healthcare system, to offer free or reduced fee services to NBCCEDP clients.Respondents reported that arrangements for treatment were made for almost all NBCCEDP clients who received a diagnosis of breast cancer or invasive cervical cancer. Respondents stated that some women experienced time delays between screening, definitive diagnosis, and initiation of treatment. State program officials reported that, according to 1992-1996 surveillance data, small numbers of clients in whom cancer was diagnosed (i.e., from three to 13 women in each state) subsequently refused treatment. Because these clients were not interviewed, it could not be determined whether financial barriers contributed to their decisions to refuse treatment or their loss to follow-up.

Respondents were concerned that the NBCCEDP did not provide funding for all diagnostic procedures and treatment for the diseases for which clients were being screened; approaches for delivering services were fragmented; and the process of obtaining resources required substantial effort at the state, local, and provider levels. Respondents reported that the continuation of every strategy for diagnostic and treatment services beyond the next few years is uncertain. Reported by: PM Lantz, PhD, Univ of Michigan School of Public Health, Ann Arbor. LE Sever, PhD, Battelle, Centers for Public Health Research and Evaluation, Seattle, Washington. Program Svcs Br, Office of the Director, Div of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, CDC.

Editorial Note: During July 1991-March 1997, the NBCCEDP provided 576,408 mammograms to women aged ≥40 years, and 3409 cases of breast cancer were diagnosed. During this same period, the program provided 732,754 Pap tests; 23,782 cases of cervical intraepithelial neoplasia and 303 cases of invasive cervical cancer were diagnosed. These totals included women referred to the program for diagnostic evaluation of an abnormal screening result. The NBCCEDP internal estimates suggested that during this period only 12%-15% of uninsured women aged 40-64 years in the United States had been screened by the program (CDC, unpublished data, 1997).

Screening alone does not prevent cancer deaths; it must be coupled with timely and appropriate diagnostic and treatment services. The Congressional mandate for

NBCCEDP requires grantees to take all appropriate measures to ensure provision of services required by women who have abnormal screening results. CDC provides funds for case management to help these women access healthcare services. To increase the comprehensive nature of the program, CDC recently approved the use of NBCCEDP funds for breast biopsies.

The results of this study indicate that state health departments and their partners in the seven states had developed a wide range of strategies for diagnostic and treatment services in the absence of program resources. However, the time and effort required to arrange and maintain these services diverted resources away from screening activities.

This study was subject to at least two limitations. First, the results were based solely on the experience and opinions of informed professionals affiliated with the program and did not include the perspectives of NBCCEDP clients. Second, the results may not reflect the program experiences in other states. Case study methods, however, are an appropriate and well-accepted approach to gaining in depth understanding of complex programs in realife situations (4). The validity of the findings was enhanced by developing standard instruments to guide the semistructured interviews, protecting the confidentiality of respondents' remarks, using interview transcripts for data analysis rather than relying on interviewer notes, and obtaining feedback concerning state summary reports from respondents.

As more women are screened by the NBCCEDP, a greater burden will be placed on participating health agencies, providers, and other partners to obtain resources for breast and cervical cancer treatment. Case management services will continue to be essential in helping underserved women overcome financial, logistical, and other barriers to receiving these services. Other long term solutions to ensure that women in the program receive necessary treatment services are being pursued.

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Ms. ESHOO. When the CDC does the early detection and the screening and something is found, do you have any certain way to set women on a path outside of that? Tell me what you do.

Ms. LEE. Yes. Yes, I will. Well, as you know, the 1990 act specifically forbade the use of Federal Government funds to pay for treatment.

Ms. ESHOO. Well, we know that. That is why the bill is——

Ms. LEE. Yes, right, and that's why you have introduced this bill. We are allowed to pay for diagnostic services, and so we do provide central diagnostic services.

Ms. ESHOO. But once you do what the 1990 legislation set up, and I'm not suggesting——

Ms. LEE. Okay, so then we diagnose.

Ms. ESHOO. [continuing] for giving you permission to go get into trouble to go beyond it. Do you have set information for women or——

Ms. LEE. Yes, we actually have a published paper because we have done a study on this. We have a partnership with our health agencies, the health agencies, the American Indian tribes, et cetera, and as part of that partnership, it is the responsibility of the State health agency to assure that all women diagnosed with cancer or a pre-cancerous condition receive the treatment that they need.

Ms. ESHOO. Well, it is not happening, but that is not your fault; it is that we haven't taken the next step. But that's instructive to me, because I don't think it is happening.

Ms. LEE. Well, we actually have a study that was published last year——

Ms. ESHOO. That says——

Ms. LEE. [continuing] that says, by and large, it is happening.

Ms. ESHOO. That they all got treatment?

Ms. LEE. Yes, except for the few, less than 10 percent of women——

Ms. ESHOO. Well, is it on a timely basis?

Ms. LEE. Yes, it is on a timely basis. There are some——

Ms. ESHOO. I'd like to see that.

Ms. LEE. Yes, I would be happy to provide you that.

Ms. ESHOO. I'm not here to question you. I'm here to question some of the outcomes and the results.

Ms. LEE. Right. We feel very good that we are getting—but the problem is, it is a very tenuous system. We really need the kind of help that your bill may provide for us. But because they have to put it together with a lot of charity, donated charity case from this provider——

Ms. ESHOO. Well, I think the system, at best, once it comes to treatment, is unpredictable Dr. LEE. Yes, absolutely.

Ms. ESHOO. It is a patchwork quilt at best—if you even want to bring the word "best" into this. I think that families and women in this country deserve much better. I mean, if we can get to the moon, we can do something about this, and we got to the moon a long time ago.

Let me go to another question, because I think I probably don't have that much time left. To Drs. Lowey and Trimble, in section 106 of H.R. 358, the Patients' Bill of Rights, it calls for the requirement of managed care providers to pay for treatment provided in the clinical trial. In your view, would enactment of such a provision expand access to clinical trails and speed up research aimed at preventing, treating, and curing cervical cancer? I mean, we are talking about screening; then we are talking about treatment. We know that a lot of the treatment isn't there or isn't paid for; there is underinsurance for it. But the fact of the matter is that we don't have a cure for this.

So, can you maybe just comment on that part of the legislation? I think it's a very important section, but I would like to know what your views are about it.

Mr. TRIMBLE. Only 2.5 percent of adults in the United States with cancer are enrolled on cancer treatment trials, and the National Cancer Institute has been working closely with a number of third-party payers to encourage them to pay for the patient care costs associated with these clinical trials. The NCI has never had the funds to pay for patient care costs. We pay for data management or some of the costs of data management.

We have had reasonable success with some of the third-party payers. We have worked out agreements with the Veterans' Administration and the Department of Defense, so that the patients that they cover can have access to our clinical trials. We have not yet been able to reach an agreement with the Health Care Financing Administration, and we have continued to work with the HMOs, but certainly we are supportive of all efforts to gain all Americans access to our trials.

Ms. ESHOO. So this would be——

Mr. COBURN. Would the gentlelady yield for a minute?

Ms. ESHOO. Well, I don't have any time to yield, Mr. Chairman.

Mr. COBURN. Well, I will be very benevolent with the time if we can.

We have a cancer patient, a survivor, who is going to testify, and I would like to ask you all if you would remain there until the rest of our committee can finish their questions, and if I can have unanimous consent to have her come and give her testimony now, because she has her flight in a very short time; otherwise, we will not be able to obtain her testimony.

Ms. ESHOO. Absolutely. Thank you for the time and thank you to the panel for your words and professionalism.

Mr. COBURN. Ms. Piker, would you mind coming forward, please, and giving us your testimony?

Mr. LAZIO. Mr. Chairman, could I just ask for unanimous consent to make a remark for about 30 seconds?

Mr. COBURN. Yes, sir.

Mr. LAZIO. I am so conflicted. I am supposed to be chairing the committee meeting across the hall right now. Just two quick remarks and they are: First of all, the need to get more adults in clinical trial, I think, is made all the more compelling because of the success in childhood cancer. The amount of children that are in clinical trials, I think it is up around the 90's, either in clinical trials or in NIH protocol hospitals, and the success rates, especially in certain leukemias, I think really bear out the fact that we need to do much better in terms of getting adults into clinical trials.

The second point is—this is really in response to Ms. Lee's comments about care for those women who receive bad news after they have gotten screening through the CDC program—is that, actually, the timeliness is much in question by a number of advocate groups, about whether they are getting the treatment in a timely manner, and whether it is done in a way that doesn't accelerate or compound the stress and anxiety that women are under.

For example, many women that we have talked to have incurred substantial debt, and we are talking about women, obviously, who are at the lower-income levels, minimum wage people, waitresses, people who have no hope of wiping out a $20,000 debt. And so I would not want to leave the impression that what we have here is a system of care that is reliable and that is timely and that does not compound the stress that women face when they find out that they have a malignancy.

Thank you, Chairman, for your indulgence.

Mr. COBURN. Ms. Piker.

STATEMENT OF LINDA GRACE PIKER, CERVICAL CANCER SURVIVOR

Ms. PIKER. Mr. Chairman, thank you for inviting me to share my experience with cervical cancer with this committee. I speak today as a cervical cancer survivor, a co-founder of a gynecological cancer support group, a cancer advocate, the Chair of the Kentucky Breast Cancer Coalition, which addresses both breast cancer and other women's cancer in the Commonwealth, and most of all, I speak as a friend and a confidante to numerous women who have been touched by this disease. I have seen the despair and the destruction that cervical cancer has caused these women, their families, and their friends. There are some stories that I'll never forget.

I'll never forget the beautiful young woman who was about 30 years old, whose physician called me and asked if I could talk to her, and when I talked to her, I was totally empty handed. She had had a pelvic exenteration at age 32. I also talked to another woman who had received the same treatment who was 40 years old. I think these are some of the treatments that nobody has any idea take place. I mean, the majority of the public does not.

And I'll never forget another beautiful young woman who came to speak to the Cervical Cancer Advisory Committee just weeks before her death, and I knew the man that was deeply in love with her and I know how much despair he went through after this.

In addition to the original diagnosis of cervical cancer, these women are at increased risk for vaginal, vulva, and anal cancers. One woman who was first diagnosed with cervical cancer, and then vulva cancer a few years later, stands out in my mind. She had the toughest exterior. But when you got to know her and you really listened to her, she had despair; she was embarrassed, and the fears were all there. She fought long and hard, but eventually she died.

These are only a few of the women I would like to represent. These deaths were needless. If diagnosed early, cervical cancer has a 5-year survival rate of approximately 90 percent. Most importantly, with proper screening and with treatment, cervical cancer is a preventable disease. We need to educate women on the risk factors for the disease, screening, and, if necessary, where to find information, treatment, and support.

In addition to the shock of being diagnosed with cancer in September 1990 when I was 44 years old, I could not understand how this could have happened. Since I was 19 years old, I had received annual Pap tests. I had had no problems. The more I read about the disease, the more confused I became, and the more frightening the issue became for me. Did I have an aggressive tumor? Would I live to see my 10-year-old son grow up? My gynecologic oncologist kept saying, "You'll be fine, Linda. You are going to have a radical hysterectomy with regular followup." Well, for about the next year, I was very frightened because I couldn't figure out why this would happen; I did everything you were supposed to do; what was happening?

And then to alleviate my fears, I happened to talk to one of the fellows who had worked with me from the beginning of my cancer, and he said, "Okay, Linda, what you really need to do is get your Pap smear slides, let's look at them, and I can tell you if it's aggressive and we will follow you more closely, and if not, this should give you some peace of mind."

Well, we had moved to Kentucky the previous year, and so I had to call my former physician's office and ask for my slides to be sent to Lexington, Kentucky. I was given the address of a laboratory in

California. When I called, there was no listing for the lab, and this was even more confusing. I just could not understand, you know, and so I called back to the physician's office and I said, "There's no listing."

Well, to shorten my long story, I found out that my physician had been sending the Pap slides to a lab in California that was allegedly closed because of poor quality assurance. Had I known the name of the lab my Pap slides had been sent to, I could have read about it, because they were named in The Los Angeles Times and The Wall Street Journal. Physicians were not liable for the Pap test; therefore, it is my understanding that some physicians decided not to notify their patients that the physicians had sent the patient's Pap slide to this lab.

My cancer was diagnosed when I had a Pap test the following year and my Pap slides were read by a different facility in Lexington. I spoke to my physician out of State about notifying other patients. We had quite a long discussion. It took me three phone calls to get to talk to the person, but my physician was not receptive to doing this at that time.

I suppose this was the crucial experience of my becoming an advocate for myself and other women. Not only do women need to be educated about the risks associated with cervical cancer, but they also need to know what questions to ask about screening methods and their laboratories.

Since 1993, I have worked in the public health arena, where I focus on ways to bring women into local health departments for breast and cervical cancer screening. I also work with health departments to eliminate missed opportunities for screening of current clients. For approximately the last 3 years, I have worked with community cancer coalitions which have unique ways to target women in their communities for breast and cervical cancer screening. Cooperative partnerships and education are key components in their success for increasing the number of breast and cervical cancer screenings in the communities.

For any education campaign addressing the issue of human papilloma virus, or HPV, a clear message will need to be presented in a sensitive manner; otherwise, an ill-conceived education campaign might well become a barrier for women seeking screening.

As I leave here today, I thank you for holding a hearing on cervical cancer. As a mom of a childhood cancer survivor and relative to friends or individuals with the various types of cancer, I often call myself the generic cancer survivor. Although I am grateful to this committee for addressing the issue of cervical cancer, I think that a more comprehensive approach to fighting the war on cancer would be more effective. I have never been a cancer survivor who wanted to fight the body part wars. I look forward to the day when we all unite and fight cancer together. Thank you.

[The prepared statement of Linda Grace Piker follows:]

PREPARED STATEMENT OF LINDA GRACE PIKER

Mr. Chairman, thank you for inviting me to share my experience with cervical cancer with this committee. I speak today as a cervical cancer survivor, confounder of a gynecological cancer support group, cancer advocate, the chair of the Kentucky Breast Cancer Coalition, which addresses breast cancer and other women's cancer issues in the Commonwealth, and, most of all, I speak as a friend and confidant to numerous women who have been touched by this disease. I have seen the despair and destruction that cervical cancer has caused to these women, their families, and friends. There are some stories I'll never forget: the beautiful young woman in her thirties who had a pelvic exenteration or the distressing call from a forty-year-old woman who had undergone the same treatment. I'll never forget one beautiful young woman who spoke to a cervical cancer advisory committee only weeks before her death or the young man who was devastated by her death. In addition to their original diagnosis of cervical cancer, these women are at increased risk for vaginal, vulva or anal cancer. One woman, who was first diagnosed with cervical cancer and then vulva cancer, stands out in my mind. She was alone, had no medical insurance, and had a low paying job prior to her illness. She had a very tough exterior, but when you got to know her and listened to her, the despair, embarrassment, and fears were all there. She fought long and hard, but she eventually died. These are only a few of the women I would like to represent. These deaths were needless. If diagnosed early, cervical cancer has a five-year survival rate of approximately 90%. Most importantly, with proper screening and treatment, cervical cancer is a preventable disease. We need to educate women on the risk factors for the disease, screening, and, if necessary, where to find information, treatment, and support.

In addition to the shock of being diagnosed with cancer, in September 1990, when I was forty-four years old, I just could not understand how this could have happened. Since I was nineteen years old, I had received annual Pap tests. I'd had no problems. The more I read about the disease, the more confusing and frightening this issue became for me. Did I have some aggressive tumor? Would I live to see my ten-year-old son grow up? My gynecologic oncologist kept saying I'd be fine. I would have a radical hysterectomy and regular follow-up. To alleviate my fears of an aggressive cancer, I called my former physician's office and asked that my slides be sent to my physician in Lexington, KY. I was given the address of a laboratory in California. When I called, there was no listing of the lab. I was even more confused. To shorten this story, I found out that my physician had been sending the Pap test slides to a lab in California that was allegedly closed because of poor quality assurance. Had I known the name of the lab my Pap test slides had been sent to, I could have read about the lab in the *Los Angeles Times* or the *Wall Street Journal*. Physicians were not liable for the Pap test; therefore, it is my understanding that some physicians decided not to notify their patients that they had sent their slides to this lab. My cancer was diagnosed when I had my Pap test the following year and a lab in Lexington read my slides. I spoke to my physician about notifying other patients, I did not feel that the physician was receptive to doing this at that time. I suppose this was the crucial experience in my becoming an advocate for other women and myself. Not only do women need to be educated about the risk factors associated with cervical cancer, but also they need to know what questions to ask about screening methods and laboratories.

Since 1993, I have worked in the public health arena where I focus on ways to bring women into local health departments for breast and cervical cancer screenings. I also work with health departments to eliminate "missed opportunities" for screening our current clients. For approximately the last three years, I have worked with community cancer coalitions, which have found unique ways to target women in their communities for breast and cervical cancer screenings. Cooperative partnerships and education are key components in their success for increasing the number of breast and cervical cancer screenings in their communities. For any education campaign addressing the issue of human papilloma virus (HPV), a clear message will need to be presented in a sensitive manner. Otherwise, an ill-conceived education campaign might well become a barrier for women seeking screening.

As I leave here today, I thank you for holding hearings about cervical cancer. As a mom of a childhood cancer survivor and relative or friend of individuals with various types of cancer, I often call myself the "generic cancer survivor." Although I am grateful this committee is addressing the issue of cervical cancer, I think that a more comprehensive approach to fighting the war on cancer will be more effective. I've never been a cancer survivor who wanted to fight the "body part wars." I look forward to the day when I can see us all united to fight cancer. Thank you.

Mr. COBURN. Thank you, Ms. Piker. I will defer any questions to the ranking member. Do you have any questions of the witness? Any other members of the committee have questions for this witness?

[No response.]

Ms. Piker, thank you for being here.

The gentleman from Tennessee is recognized.

Mr. BRYANT. Thank you. Let me add my appreciation, Ms. Piker, before you go back to Kentucky, I assume, for your being here and also for the very learned panels that we have had here.

At this time, I have been asked by the chairman if I would yield my time to the chairman. I would be happy to do that.

Mr. COBURN. I thank the gentleman. I just have a couple other questions that I kind of want to follow up on. I introduced into the record a few moments ago a letter we received on the 19th from Dr. Klausner. The testimony today—we have two different testimonies. One testimony is that a condom is effective in HPV, and one that says it is not. I wonder if any of the panel would help this committee know what this answer is to that question. Anybody have an answer for that?

Mr. VALDISERRI. Let me start. I think it's an extremely important question, and I think it is easy to understand why there might be some confusion on it.

What we know in general—and I'm talking generally now; I'm not talking about HPV—but what we know in general about condoms and viruses lead us to believe that the condom has at least a theoretical possibility of preventing transmission if the lesion is confined to the penis that is covered by the condom. Now, there are a lot of "if's." Obviously, there are a lot of "if's" and conditions. Given that HPV infection may not result in a visible lesion and that typically that there are multiple sites of infection on the genitalia, I think that what you will see in most of the articles or textbooks or review articles is the statement that there have not been definitive studies, prospective studies, that have evaluated condom efficacy in terms of preventing HPV. So, I think that's why there is that confusion.

Mr. COBURN. I would quote Dr.—and you don't have the benefit of this letter, but Dr. Klausner states additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted. And he states in his letter why it's not. It's because if you, in fact, are infected, the scrotum is infected as well.

If I could make one point, you all are behind the curve on this. The epidemic is way ahead of you. Is that not really true? I mean, the epidemic associated with evasive HPV and cervical dysplasia is ahead of where we are. We really don't have the knowledge on this sexually transmitted disease that we have on many others. Is that a fair statement?

Mr. VALDISERRI. In some areas, I would agree with certain aspects of that statement. Definitely in terms of some of the condom efficacy studies and, as we discussed earlier, in terms of some of the surveillance information, especially about specific types of HPV.

Mr. COBURN. I guess if I had my heart of hearts, what I would want everybody to know is that we really don't know all the answers right now about HPV and that there is an epidemic of dysplasia out there. All you have got to do is ask any pathologist what they are seeing in their Pap labs. I mean, it is growing like crazy right now. We are seeing tons of carcinoma in situ, and I know the studies are ongoing in that.

The fact is, we don't know. We have an unknown quality right now. As we talk about access, there is not one woman that I don't want to have access to a high quality Pap smear and physical exam every year. I want that for every woman in this country, those that have been sexually active and those that have not. But I also want them to have the knowledge about what the danger is of this disease.

I mentioned earlier a Green Journal study in 1987 or 1988, where they did culture HPV, one of the aggressive serotypes from amniotic fluid, where they do, can culture this same virus in the reproductive tract of newborn babies, male and female, it is an important consideration that our highest institutions have not aggressively researched.

And so, my point—and I'm going to submit a list of questions, and they will be given to each of you and then I'll ask that we divide those up to the appropriate—actually, I'll try to get them divided up to the appropriate expert that we have here today.

You know, we really ought not to worry about where we have been, but we really ought to get busy about where we need to go on human papilloma virus. I have been in practice 16 years. I have never seen anything like it in my office. And if you go talk to practicing physicians that are in the middle low-income and with teenagers and Medicaid patients, we are seeing an explosion of this disease right now. And it is aggressive types. I mean, we are seeing a ton of high-grade dysplasia.

So, my wish is that, tell us what we need to do so that we really know what the science is, because I don't believe it's out there right now.

Mr. VALDISERRI. I don't want to be parochial, but I couldn't agree with you more. I do want to say, again, that we have been working at CDC and our center and with our colleagues on trying to develop a specific plan focused on—we looked first at herpes, which is not, obviously, not the focus of this meeting, but now we are doing the same thing with HPV. We have this big meeting in April with a lot of experts coming in and we have actually generated close to 45 specific questions that we want these people to grapple with.

So, I couldn't agree with you more, Dr. Coburn, that there are still some issues that we have to invest in getting answers to.

Mr. COBURN. Before I would yield to anybody that would like additional time—we know that a condom is not preventive. I mean, we know that right now. Unless we wrap everybody in saran wrap, we are not going to prevent human papilloma virus.

Mr. VALDISERRI. And we also know that there is more than HPV as a sexually transmissible disease. So we have this complex issue of—it is not an issue if people are abstinent, but we have this complex issue for people who are sexually active, where condoms can be helpful in preventing other STDs. How do we craft the message so that they know that it might not necessarily protect against HPV? And then they will say, "Well, gee, why even bother?"

Mr. COBURN. Very easy. It is a condom won't protect you from human papilloma virus, the No. 1 cause of cervical cancer in this country, and it affects 50 percent of those people who are sexually active, regardless that it might protect you from HIV. If it won't protect you from the No. 1, then it's a false safe sex message. It doesn't work. And so we can continue down that line of false assumptions, but you are going to find the science that will say it doesn't work, and we know it doesn't. The practicing physicians out there today know it doesn't work.

So, all I'm saying is, we need to look at the data completely from a pure scientific—and give us a plan to where we can give treatment, whatever we do. I treat kids who are going to be sexually active, if they tell me they are; I give them very tool I can. But the point is, is we can't send a false message about HPV.

Mr. VALDISERRI. Well, we don't intend to send a false message.

Mr. COBURN. Thank you. And the ranking member, Mr. Brown.

Mr. BROWN. Mr. Chairman, I'm a little concerned about the sort of exchange and the questions, the letter you have submitted, and I'm glad that we finally got a copy of it. I understand, from what you just said, you will submit some more questions of this panel. I would hope that this subcommittee would—and I don't lay the blame at your feet and I appreciate your genuineness about this—but would see fit to share with the minority some of this information. This letter, it started off—you posed 15 questions about the possible relationship of induced abortion to breast cancer; these are pretty volatile issues that people have very strong feelings about. I know, it's more than that; I understand that, but that was the lead sentence in it. We just found out about this a month after it was received by Mr. Bliley.

I would just like to encourage this subcommittee on the majority side to make sure the minority, particularly when we are talking about issues that people care about and the discussion you had with Dr. Valdiserri, just now, that we have this information ahead of time.

Mr. COBURN. Mr. Brown, the staff tells me that you all received a copy of that letter the day it was sent.

Mr. BROWN. My understanding from our staff is that we received the letter that you sent to the doctor, that Chairman Bliley sent to HHS, but we have not gotten the response until today.

Mr. COBURN. If, in fact, you didn't, that is a grave error that should be corrected by this committee, and you should have the response and any letter that comes to this committee, based on a letter from it. As you know, I am not in the position to empower that that happens each time.

I would just like to ask if any of the other members of this panel would like to offer anything for us, tell us where we know what we need to do, make recommendations outside of what you have made in your testimony.

Mr. VALDISERRI. May I just again say, please don't forget, in addition to the basic research needs, don't forget the whole host of operational research questions; and that's fairly parochial, because it is what we tend to do at CDC. But our last interchange about how do you craft a message for sexually active people, about what condoms can and can't do, given that in the real world there are many, many STDs, as a perfect example of the kind of work that is very important—so, I would like to, again, go on record saying that that is a need that we have.

Mr. COBURN. The gentlemen from New York is here. Would you like to ask questions, Mr. Towns? Yes, the gentleman is recognized for 5 minutes.

Mr. TOWNS. Thank you very much, Mr. Chairman.

What population is considered to be at high risk for developing cervical cancer? Anybody?

Ms. LEE. There are lots of risk factors. Probably the strongest risk factor that is sort of the cause of it is what we have been talking about today, which is infection with certain subtypes of human papilloma virus. Another very important risk factor is failure to be regularly screened with Pap smears. Then, you find higher rates of cervical cancer developing, and women dying from it, in foreign-born women in the United States and women who are Hispanic, who are African-American, and who are from certain subpopulations from Asia. You also find cervical cancer to occur, and especially cervical cancer deaths, to occur more often in older women.

Mr. TOWNS. Decreasing the incidence of cervical cancer 30 percent, is that dependent on treatment, new treatment methods, or——

Ms. LEE. Most all of that is probably because of Pap screening and you identify the pre-cancerous condition. It is easily treated in almost all instances. You cure it and then the woman never develops cervical cancer, and therefore, then she doesn't get counted as a cancer statistic. And she doesn't have it, either.

Mr. TOWNS. Are the new treatment methods for cervical cancer considered experimental, or are the likely to be widely accepted by the insurance companies as a new standard of treatment?

Mr. TRIMBLE. There have now been five studies, of which three have been published in the medical literature. We think that they will be considered as standard of care, and insurance companies will reimburse for their use.

Mr. TOWNS. Any other comments on that from anybody else?

[No response.]

Have we solved the lab certification issue or do we need to promote something comparable to the mammography quality standards act for Pap smears?

Ms. LEE. I am not sure any of us are really up on that. I think that the CLIA Act—I can't even come up with what that acronym, Clinical Laboratory—oh, yes, you know that; thank you. It was designed—and I'm not very much up on this—but it was designed, as one of the motivating reasons for its passage back, I think last decade, was because of problems with Pap screening; and whether is solved it or not, I am not equipped to tell.

Mr. TOWNS. Well, let me just say, first of all, Mr. Chairman, thank you very much and let me thank all of you for your testimony. I am sorry I was not here when you actually testified, but I did read almost all the testimonies; I want you to know that, and I do plan to read all of them. I was involved in another meeting is the reason I was not here; because I am very interested in this. You know, I come from a family of four and I lost my entire family, except myself, from cancer. So, I'm always very interested in terms of learning as much about this as I possibly can. I lost my mother, father, and a brother from this disease. So I am very interested in what you have to say.

So I will be reading all the material, and I really appreciate the time and the effort you have taken to come here to share with us, as well. Thank you so much.

Mr. COBURN. The gentleman yields back.

I have two things. Dr. Lee, would you note for the record when we asked you a question, cancer, under the definition of those cases, does that include carcinoma in situ or not? In terms of the incidents that you all are quoting, is that quoting including carcinoma in situ as well as invasive cancers?

Ms. LEE. From our program, you mean?

Mr. COBURN. Yes.

Ms. LEE. No.

Mr. COBURN. It is invasive cancer only?

Ms. LEE. The 508 are invasive only, and the carcinoma in situ's are actually folded in with the CIN-3's.

Mr. COBURN. All right. The other question I would ask, if you would, in response to Mr. Towns' question, the new epidemiological data that I am seeing is saying that the cancer now is occurring in earlier and earlier and younger and younger women. And, in answer to his question, your response was it is actually in older women. Would you mind forwarding any new material that you have to this committee, in terms of trends, epidemiologically?

Ms. LEE. Sure.

Mr. COBURN. The friends I have across the country that are practicing medicine, what they are seeing and what they are saying is that this is a disease that is moving to young women.

Ms. LEE. Actually, what I said was the cervical cancer deaths are highest in the older women. In fact, the people from the NCI collect the good data on this, and we have looked at it quite a bit. The rate of cervical cancer among women under 50, the new diagnoses are actually going down. I looked at it the other day. They are going down, based on seer data.

Mr. COBURN. Okay. Thank you very much. We have one additional question.

Mr. BROWN. I'm sorry to keep you here for the rest of the evening, but, Dr. Lee, you in your testimony mention approximately half the inaccuracies—you said that the Pap test is far from 100 percent accurate; approximately half of the inadequacies are due to an inadequate collection of the Pap smear by the provider, and the other half are due to errors at the laboratory. And I know your expertise is not centered around this, but does it make sense for us to pursue perhaps the MQSA model, where there is inspection once a year, except for those who have a record of doing very, very well, inspection of facilities once a year? I don't know if inspection is the key, or working with, actually re-training of the people regularly, the technicians, all of that, re-licensing, some of the things that MQSA does. Is that something we should consider here?

Ms. LEE. That's really something that I am not totally expert in. I will tell you this: that the majority—and some people might even call the substantial majority—70 to 80 percent of all new cervical cancer cases occur in women who have not been screened in the last 5 years. The issue: There are lab errors, and Ms. Piker was one of those unfortunate people. There are lab errors, but that is not where the bulk of the problem is. And so I will put to you that I think, until we have something wonderful like an HPV vaccine, that we can use to prevent, or other therapies, that our biggest, the most important thing is to continue to go out and try to find women who aren't being screened. Because if we spend a lot of time trying to improve the collection, we are still going to only maybe be affecting up to 20 percent, and not the other 80 percent.

Mr. VALDISERRI. To comment on that, there is a part of CDC that deals specifically with these issues, our Public Health Practice Program Office, and when we go back I will talk to their Division of Laboratory Systems—they have been involved in the implementation of CLIA—and see if they have any specific information, both related to what Mr. Towns asked and what you have asked. There may be some data; we just don't have it at our fingertips. It does make the point, though, that you always need to remember provider education, even when you get all these other issues taken care of.

Mr. COBURN. Let me thank the panel again for being here and persisting with us. I appreciate your input.

I would just make one last comment, Dr. Valdiserri: that the providers in this country are way behind where they need to be in terms of diagnosing STDs. We need to have a good national effort to bring them back up. And thank you again.

We will bring forward the third and final panel, and I wish to apologize for the length of your wait. Dr. John Thomas Cox from the University of California in Santa Barbara California, and Dr. Sharyn Lenhart, and Rosemarie Gatshca—I like that name—that's great—from the American Society of Clinical Pathologists.

Dr. Cox, if you would care to start and, if you could, be as brief as possible with your testimony, so we can spend as much time as we can discussing it.

STATEMENTS OF JOHN THOMAS COX, STUDENT HEALTH SERVICES, UNIVERSITY OF CALIFORNIA AT SANTA BARBARA; SHARYN LENHART, IMMEDIATE PAST PRESIDENT, AMERICAN MEDICAL WOMEN'S ASSOCIATION: AND ROSEMARIE GATSCHA, CYTOLOGY MANAGER, AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS

Mr. COX. Chairman Bilirakis, Dr. Coburn, members of the House Subcommittee on Health and the Environment, my name is John Thomas Cox, and I am director of the Women's Clinic, University of Southern California in Santa Barbara, Chair of the steering committee of the National Cancer Institute-sponsored ASCUS LSIL trial, also known as ALTS, and Chair of the Practice Guidelines Committee of the American Society of Colposcopy and Cervical Pathology.

I wanted to express my thanks to you for providing me the opportunity to present a clinical perspective on the issues related to women and cervical health as I see it in 1999. In the interest of time, the following comments are a markedly shortened version of my written statement, and I will not be discussing the many positives of the Pap smear screening program, as has already been mentioned here today. But I do want to mention some of the factors that we run into as clinicians, and I know, Dr. Coburn, you run into them as well.

Despite the positives of the Pap screening program, the following problems loom large: that while the majority of cervical cancer develops in the segment of the population that remains unscreened, approximately 6,000 women develop cervical cancer annually, who have had reasonable, if not all perfect, Pap smear screening. And, although the incidence of cervical cancer and associated mortality has decreased over 40 percent since 1973, these numbers have remained constant for over a decade. Additionally, since 1986, there has been an annual 3 percent increase in the incidence of invasive cervical cancer in white women under the age of 50. And now, this is the first information I have had that that has now ceased to increase.

The risk of missing disease in the screened population is attributed primarily to false negative cytology. The false negative rate of the Pap has been variously estimated to be from 2 to 50 percent. However, the Agency for Health Care Policy Research just released the evidence report, technology assessment entitled, "Evaluation of Cervical Cytology," which estimated the true sensitivity of the Pap to be just 0.51. Their conclusion was that, "Despite the demonstrated ability of the cervical cytologic screening in reducing cervical cancer mortality, the conventional Pap test is less sensitive that it is generally believed to be." Because of the concern over the risk of missing disease, the medical community has responded by pursuing the diagnosis and followup of the most minimal cellular atypia on the pap. The resulting loss in specificity brings exceptional numbers of normal women in for further evaluation. The cost in dollars and distress of evaluation of approximately 2 million women given the borderline reading of ASCUS has been very high. The result is an excessively expensive, approximately $6 billion, screening program fraught with the risk of over-diagnosis, overtreatment, and increased psychological burden.

So, I think we need to work on solutions. First, of course, we need to start with education, which we have talked a great deal about today. Education and outreach, especially to populations particularly reluctant to attend screening clinics, must be placed at highest priority, since the failure to draw the unscreened portion of the population in for routine Pap smears remains the most common reason for development of cervical cancer. The nature of failure of women to get adequate screening is not well understood, and is likely to be the result of a complex milieu of cultural, societal, and educational factors. Intense efforts will be necessary to understand the reasons women do not get Pap smears, or do not return, as directed, for followup.

Additionally, women receiving cervical screening should be educated about the ideology of cervical cancer and the reasons for doing Pap smears, including the association with HPV. Education must extend to the healthcare providers as well, as outreach is doomed to failure without a well-informed and empathetic health services sector.

Second, we need a more efficient screening system, and there will be some controversy over this, but I think we need to talk about it. The limitations of cervical cytology in the screening system requires a reappraisal, with the following deserving our utmost attention. We need to ask whether beginning screening at age 18, as now recommended, is the best way to spend our cervical cancer screen resources, since this is an age in which cervical cancer is virtually non-existent, but transient HPV manifestations are very common.

Additionally, the inability of caregivers to accurately predict which women are low risk continues to foster annual screening. We will never be able reduce the cost of the screening system until we can safely increase the screening interval. In order to safely increase the screening interval, we will need to reduce the risk of missed disease. New technologies have been developed to improve the sensitivity and efficiency of detection of cervical disease. These include liquid-based thin layer cytology, automated computerized analyzers, and tests for the presence of HPV. Despite increasing evidence that many of these new technologies are already improving the effectiveness of cervical cancer screening, or hold great promise in the future, availability of the patient has been severely eliminated.

In order to improve the efficiency of the system, we must find the most efficient and patient acceptable manner of evaluating ASCUS paps. The NCI ALTS study is designed to provide a clear understanding of the advantages and disadvantages of various options for the followup of women given the Pap reading of ASCUS or LSIL low-grade squamous intraepithial lesion. This study should settle the question once and for all, whether women given this Pap reading are best referred immediately to colposcopy, best followed by several repeat paps at accelerated intervals, or best tested for HPV and referred to colposcopy only if the HPV test is positive.

Finally, the present intense public interest in healthcare quality issues includes questions regarding who should make decisions about how effective cervical cancer screening will be, and by what measure should effectiveness be evaluated. Until now, new cervical screening technology assessments, which have influenced public policy, have focused almost entirely on the single end-point of cost-effectiveness as measured by cancers prevented and lives saved.

In contrast, women deserve that cervical cancer screening policy be set by a much fairer model, that encompasses quality-of-life issues associated with decreasing the ambiguity of equivocal paps and with earlier detection of disease. This would include reproductive implications and reductions in invasive treatments, patient anxiety, and loss of time from work and childcare.

We must acknowledge the individual patient's interest in receiving information about the benefits, risks and costs of traditional Pap followup compared with new cytology screening enhancements. Women have a right to be routinely informed of these issues and to participate in decisionmaking regarding their health choices.

And, thank you for the opportunity to address these issues, and I will be pleased to answer any questions that you may have.

[The prepared statement of J. Thomas Cox follows:]

PREPARED STATEMENT OF J. THOMAS COX, DIRECTOR, WOMEN'S CLINIC, UNIVERSITY OF CALIFORNIA, SANTA BARBARA

Chairman Bilirakis, members of the House Subcommittee on Health and the Environment, my name is John Thomas Cox, MD. I am Director of the Women's Clinic at the University of California in Santa Barbara, Chair of the Steering Committee for the National Cancer Institute sponsored ASCUS/LSIL Triage Study (ALTS) and Chair of the Practice Guidelines Committee of the American Society of Colposcopy and Cervical Pathology. I want to express my thanks for providing me the opportunity to present a clinical perspective on the issues related to women and cervical health as I see it in 1999.

The Positives of Cervical Cancer Screening

In countries without cervical cancer screening, cervical cancer remains first or second amongst all cancers in women in both incidence and mortality. The measure of success of the Pap smear screening program in countries fortunate enough to have such a program, such as the US, is relegation of cervical cancer to the 6th commonest cancer amongst women and the 10th leading cause of cancer death. These decreases in the US are so dramatic that Pap smear screening is one of the few interventions to receive an “A” recommendation from the U.S. Preventive Services Task Force even though there have been no randomized trials demonstrating its effectiveness.

Problems with the Cervical Cancer Screening Program

Approximately 14,000 women develop cervical cancer in the US annually and approximately 5000 die of the disease. While the majority of cervical cancer develops in the segment of the population that remains unscreened, approximately 6000 women develop cervical cancer annually who have had reasonable, if not all perfect, Pap smear screening. The lifetime likelihood that a women never screened will develop cervical cancer is 3,748 women per 100,000 (3.7%), but even with annual screening approximately 305 per 100,000 women (0.3%) will develop cervical cancer during their life. Although this dramatic drop in incidence demonstrates the remarkable effectiveness of the Pap screening program, nevertheless this is a toll that is individually agonizing for both patient and for care-giver. Even though the incidence of cervical cancer and associated mortality have each decreased over 40% since 1973, these numbers have remained fairly constant for over a decade. Additionally, since 1986 there has been an annual 3% increase in the incidence of invasive cervical cancer in young white women under the age of 50.

These statistics highlight both the success of cervical cytologic screening and the fact that, like any other test, achievement will never reach a perfect score. The risk of missing disease in the screened population is attributed primarily to false-negative cytology. The false-negative rate of the Pap has been variously estimated to be from 2% to greater than 50%. In January, 1999 the Agency for Health Care Policy and Research (AHCPR) released the Evidence Report/Technology Assessment, “Evaluation of Cervical Cytology”. Using a stringent meta-analysis of published studies comparing cervical cytologic diagnosis with clinical diagnosis based on colposcopy or biopsy, the AHCPR provided an estimate of the true sensitivity of the Pap to be 0.51. Their conclusion was that “despite the demonstrated ability of cervical cytologic screening in reducing cervical cancer mortality, the conventional Pap test is less sensitive than it is generally believed to be”.

Such statistics are in direct conflict with the public perception that the Pap smear is, or should be, an infallible test. The result in failed expectations is exceptional medicolegal liability related to the development of cervical cancer in any women with a history of previous cervical screening. For this reason, failure to diagnose cervical cancer is the second leading cause of liability losses for gynecologists and the leading liability for laboratories even though revenue from cytology accounts for only a small fraction of total laboratory income.

While false-negative cytology accounts for the majority of failures in the screened population, the poor specificity of cytology may be a greater problem for both the individual and society. The low rate of cervical cancer makes the risk of missing disease statistically small for each individual patient and for each Pap. However, the reality of the imperfect nature of the test looms large for both the laboratory personnel reading the Pap and for the caregiver. When the threshold for evaluation of a woman with an abnormal Pap is set very high, i.e. a high-grade or HSIL Pap, the specificity of the Pap is very good. That means that disease with significant threat to the woman is likely to be found on further evaluation. However, in order to protect our patients and ourselves from the vicissitudes of missed cervical cancer, the medical community has responded by pursuit of even the most minimally atypical cells. When the threshold for evaluating women with an abnormal Pap is set low, specificity falls dramatically. This means that many normal women will be evaluated for minimally abnormal Paps. The result is an excessively expensive (6 billion dollar) screening program fraught with the risk of overdiagnosis, overtreatment, and increased psychological burden. While all who have taken the Hippocratic Oath desire to do anything and everything possible to prevent an untimely loss of life, we must admit that much of our response to minor cytologic abnormalities has developed less out of reason than out of fear of liability.

Solutions

How can we penetrate this impasse in the further reduction in cervical cancer incidence and mortality? Will attempts to further reduce the rate of cervical cancer make the system unaffordable? Should we "tinker" with the present system or is there reason, or promise, to justify a major re-evaluation of how we approach cervical cytologic screening and follow-up to abnormal Pap smears? How can we motivate the unscreened population to obtain good cervical health care? I believe that the answers to these questions can be found by vigorous pursuit of the following:

Education

Education and outreach, especially to populations particularly reluctant to attend screening clinics must be placed at highest priority since the failure to draw the unscreened portion of the population in for routine Pap smears remains the most common reason for development of cervical cancer. While financial barriers are often cited as a major reason in limiting access to cervical screening, most studies have concluded that cost plays a minor, almost insignificant role. For example, Canadians, for whom all health care coverage is provided, have non-compliance patterns nearly identical with those of patients in the United States. Additionally, approximately 60% of women getting cervical cancer in one of the largest prepaid HMOs in the U.S. had not received adequate Pap smear screening even though a large percentage of these women had seen their primary care physician in the recent past. These statistics highlight the complex nature of failure of women to get adequate screening, which is likely to be the result of a complex milieu of cultural, societal and educational factors. Education must extend not only to women in the unscreened population, but women already being screened and to their caregivers. Intense efforts will be needed to understand the reasons for failure to attend screening and to apply the resources necessary to overcome these barriers.

Additionally, women receiving cervical screening should be educated about the etiology of cervical cancer. In 1995 the Agency for Research in Cancer and the World Health Organization (WHO) proclaimed cervical cancer to be the virtually exclusive result of the long-term persistence of human papillomavirus (HPV). Education must extend to health care providers as well, as outreach is doomed to failure without a well-informed and empathetic health services sector. Women must be made aware of the etiology of cervical cancer and its precursors, and, thereby, of the reason for which Pap smear screening is performed. Discussion of the sexually transmitted nature of the process cannot be avoided. However, it must be done without prejudice and with great care, compassion, and reassurance given that although the virus is extremely common, the risk for the development of cervical cancer is very low, especially with conscientious Pap smear screening. Clinicians must be continually reminded of the importance of cervical cancer screening so that women attending for medical care for other reasons may yet obtain a Pap smear in what may be their only encounter with the medical community.

A More Efficient Screening System

Taking a new look at what is generally considered to be a successful system is never without controversy. However, the limitations of cervical cytology and the screening system requires a reappraisal, with the following deserving our utmost attention.

1). *Optimal age to begin screening and optimal screening interval:* The pattern of practice in cervical cancer screening has been largely unchanged for 50 years. Annual Paps beginning at age 18 or within one year of beginning sexual activity, whichever comes first, remains the standard of care even though ACS and ACOG guidelines provide the option to extend the screening interval to 3 years in women considered at low risk. Concerns regarding false-negative cytology, medicolegal liability and the improbability of being able to accurately predict which women are really at low risk has served as the major impediment to implementation of prolonged screening intervals. Additionally, due to the high-prevalence of HPV and its induced cytologic changes in young women, a significant portion of the funds available for cervical cancer screening are spent on diagnosis and treatment of a commonly transient manifestation at little to no immediate risk of cervical cancer, and low long-term risk. While it is very important to test for sexually transmitted diseases (STDs) in this age group, the peculiar characteristics of HPV may not make Pap screening in very young women the most prudent approach.

In order to provide the safest, yet still cost-efficient coverage, we must consider redirecting the greatest concentration of our cervical cancer screening resources to those populations at greatest risk and least likely to be traumatized unnecessarily by medical intervention. This may require beginning screening at a somewhat later age and extending the screening interval. However, safely extending the screening interval would require greater reassurance than that provided by a screening test with just over 0 .50 sensitivity.

2). *Reducing the risk of missed disease:* New technologies have been developed to improve the sensitivity and efficiency of detection of cervical disease. These include liquid-based thin-layer cytology, automated computerized analyzers, and tests for the presence of HPV. False negative Paps are generally very difficult Paps to read, often with very few abnormal cells, and often compromised by obscuring inflammation, blood or other exudate. Liquid-based cytology eliminates much of the potential for obscured Paps and may provide a more representative sample. Computer analyzers have been approved for both primary review of the Pap and for CLIA mandated rescreening. HPV testing as an adjunct to the Pap smear in women over the age of 30, who are less likely to be positive for HPV in the absence of cervical disease, would appear to increase the negative predictive value of the screen to approximately 97% without flooding the system with normal women. Yet, despite increasing evidence that many of these new technologies are already improving the effectiveness of cervical cancer screening, or hold great promise in the near future, availability to the patient has been severely limited. The reasons for this are quite clear. In the present managed care environment it is not sufficient to prove increased efficacy. Increasingly, the interests of third-party payers have dictated the interaction between clinician and patient. There is now the opportunity to make a significant impact on both the loss of life and on the inefficiency of the cervical cytology screening program if we have the will and the foresight to integrate the best that these technologies provide. If we do not, the present impasse in further reduction in cervical cancer will remain, and the commercial viability and future availability of these major improvements will be lost. Much not only depends upon the willingness of third-party payers to cover appropriately effective emerging technologies, but also upon a full understanding by clinicians of their potential and the willingness to discuss the new methods with their patients.

3). *Providing the most objective and efficient triage of women with equivocal Paps:* The NCI/ALTS Study is designed to provide a clear understanding of the advantages and disadvantages of various options for the follow-up of women given the equivocal Pap smear reading of atypical squamous cells of undetermined significance (ASCUS) and the more diagnostic reading (for the probability of association with HPV) of low grade squamous intraepithelial lesion (LSIL). The follow-up options being evaluated include a). Immediate referral to colposcopy of all women with ASCUS or LSIL Paps, b). Repeat Pap until the woman has obtained 3 or 4 normal follow-up Paps with referral to colposcopy if any repeat is abnormal, or 3). Testing for the presence of HPV and referral to colposcopy only if the test is positive for an HPV type known to be associated with high-grade cervical precancers and cancer. Until this time there has been substantial disagreement amongst the medical community regarding which of these options is best. Recently, however, the availability in research settings of Hybrid Capture II, a new HPV test with improved sensitivity has provided very favorable results as a triage option for ASCUS. The comprehensive, randomized protocol of the ALTS Trial should once and for all settle the question of which follow-up option is most reliable, most cost-efficient, and, perhaps of greatest importance, most acceptable to women.

4). *Evaluating the cost-effectiveness of cervical screening options:* The present intense public interest in health care quality issues includes questions regarding who should decide how effective cervical cancer screening will be, and by what measures should effectiveness be evaluated? Two important technology assessment reports have recently been released; the report of the Technology Evaluation Center of the Blue Cross and Blue Shield Association (April, 1998) and the AGOG Committee Opinion: New Pap Screening Techniques (August, 1998). Both emphasize the group perspective on cost-effectiveness, almost to the exclusion of, or even acknowledging the individual patient's interest in receiving information about the benefits, risks, and costs of traditional Paps compared with new cytology screening enhancements. Unfortunately, cost-containment analysis has focused only on reduction in death from cervical cancer. Considering the already relatively low rate of cervical cancer, this is an endpoint doomed to show insignificant changes in increased life expectancy when factored over the entire population of women screened. A much fairer model for women is one that takes into account all the factors of cervical cancer screening that affect their lives. This would encompass quality-of-life issues associated with earlier detection of disease, including reproductive implications, and reductions in invasive treatments, patient anxiety and loss of time from work and childcare. In addition, cost-benefit analysis includes an evaluation of the benefits derived for both patient and caregiver of reducing and clarifying the nature of borderline Pap readings and obscured or otherwise compromised specimens that result in unnecessary repeat visits. Women have a right to be routinely informed of these issues and to participate in decision-making regarding their health choices.

Again, thank you for the opportunity to address these issues. I will be pleased to answer any questions that you may have.

Mr. COBURN. Dr. Lenhart.

STATEMENT OF SHARYN LENHART

Mr. LENHART. Thank you. Good afternoon, Mr. Chairman and members of the subcommittee. My name is Dr. Sharyn Lenhart. I am the immediate past president of the American Medical Women's Association, and I also chair AMWA's Advisory Committee to the National Cervical Cancer Public Education Campaign.

The American Medical Women's Association or AMWA is a national multi-specialty organization comprised of more than 10,000 women physicians and medical students. As a leading advocate for women's health issues since 1915, AMWA members have advocated for Federal legislation, influenced local policy, developed physician education programs, and spearheaded national consumer education campaigns to ensure that women patients and women physicians maintain a voice in upholding the highest standards of care as they relate to women's health.

AMWA believes that there is an important role for the Federal Government to play in improving women's health. We believe that this role can be fulfilled through Federal legislation that recognizes the need for women to understand how they can prevent and detect cervical cancer, and through legislation which supports adequate coverage of cervical cancer screening technologies, treatments, and preventative measures. Medicare reimbursement for Pap tests isn't adequate currently to cover the costs of providing laboratory services and should be increased to ensure the continued availability of this primary screening device.

Each year in the United States approximately 15,000 women are diagnosed with cervical cancer and 5,000 United States women die of the disease. Since the introduction of the Pap test almost 50 years ago, cervical cancer rates have been reduced by 75 percent. The majority of cervical cancers now occur in the minority of women who are not adequately screened. Two-thirds of cervical cancers occur in women who have not been screened and who constitute minority groups, by and large.

Despite the enormous success of the Pap smear, however, one-third of preventable cervical cancer occurs in women who have had a Pap test, at least in the last 5 years. Because cervical cancer is a slowly progressing cancer, often taking 10 to 15 years to develop, regular Pap smear screening, combined with new and cutting-edge screening tools, can lead to greater success in prevention.

The success of cervical screening is that it detects abnormal cells which can be treated before an actual cancer develops. Recent clinical studies have confirmed that the human papillomavirus, HPV, is the primary cause of cervical cancer. HPV is a very common virus which can infect any man or woman who has ever had sexual intercourse. In most cases HPV is harmless and asystematic. It is estimated, however, that up to 80 percent of women in the United States contract the virus at some point during their lives. Only a few of these women, those with persistent HPV infection of a high-risk type, will develop cervical cancer.

Seventy types of HPV have been identified and approximately 13 of those are high-risk. The ability to identify the precedents of the high-risk cancer groups or HPV groups may be the key in our efforts to combat this disease. Unfortunately, a recent survey confirmed that 70 percent of women are unable to name the cause of cervical cancer. While women should receive regular Pap smear screening, 2 million of these screenings produce borderline results, and another 1.5 million produce abnormal results. Recent studies have shown that as a followup to borderline Pap smear results, the use of enhanced screening technologies, including a new test that detects the presence or absence of the HPV, can give a woman's health provider added information about the cause of her borderline results. Follow-up options can then be tailored appropriately.

AMWA believes that cervical cancer can be the first major victory in the war against cancer. We believe that, in order to achieve this victory, American women and their providers need more education about cervical cancer, the importance of regular Pap smear screening, appropriate enhanced screening technologies, treatment modalities, and current and cutting-edge tests for the causes of cervical cancer. As an organization of women physicians, AMWA recognizes the crucial role we play in leading the fight against this cancer. We are more likely to provide Pap smear screening, inform our patients about cervical cancer, and encourage routine screening.

Essentially, the battle against cervical cancer can only be won with a twofold strategy of increasing the number of well-educated, pro-active women consumers and enlisting the help of physicians who encourage and provide routine screening. AMWA views the Pap smear screening as a critical device in detecting cervical cancer. We also regard enhanced screening technologies and HPV testing, in the event of a borderline Pap smear result, to be an effective way to provide healthcare providers with important additional information.

To this end, we have become a lead partner in the National Cervical Cancer Public Education Campaign. The Campaign is a collaborative educational effort involving representatives from leading women's health and civic organizations designed to inform women about the link between HPV and cervical cancer, to reinforce the importance of regular Pap smear screening, to introduce them to new and existing methods to detect cervical cancer, and to empower them to take an active role in discussing the disease with their healthcare providers. The goal of the Campaign is to reduce the number of preventable deaths caused each year by cervical cancer through increased education and outreach.

Mr. COBURN. Dr. Lenhart, can you summarize?

Mr. LENHART. Yes. AMWA calls on Members of Congress to demonstrate their support for public education about cervical cancer by signing on as co-sponsors of the Cervical Cancer Awareness Resolution and the Breast Cancer Treatment Act.

The key to winning the fight against cervical cancer is early detection. We can screen for it; we can test for HPV, and we can treat it. No woman in this country needs die from cervical cancer. If we all do our part, we can make this a reality. Thank you.

[The prepared statement of Sharyn Lenhart follows:]

PREPARED STATEMENT OF SHARYN LENHART, IMMEDIATE PAST PRESIDENT, AMERICAN MEDICAL WOMEN'S ASSOCIATION

The American Medical Women's Association (AMWA) is a national medical organization comprised of more than 10,000 women physicians and medical students. A leading advocate for women's health issues, AMWA is dedicated to improving the quality of women's healthcare. Since 1915, AMWA members have advocated for federal legislation, influenced local policy, developed physician education programs, and spearheaded national consumer education campaigns to ensure that women patients and women physicians maintain a voice in upholding the highest standards of care as they relate to women's health.

AMWA believes that there is an important role for the federal government to play in improving women's health. We believe this role can be fulfilled through federal legislation that recognizes the need for women to understand how they can prevent and detect cervical cancer and through legislation which supports adequate coverage of cervical cancer screening technologies. Currently, Medicare reimbursement for Pap tests is inadequate to cover the costs of providing laboratory service. Reimbursement should be increased to adequately cover costs, ensuring women have access to the most effective technology for detecting cervical cancer. The majority of deaths from cervical cancer are unnecessary and preventable.

THE SCOPE OF THE PROBLEM

Each year in the United States, approximately 15,000 women are diagnosed with cervical cancer and 5,000 women die of the disease. Since the introduction of the Pap test over forty-five years ago, U.S. incidences of cervical cancer have been reduced by 75%. The majority of cervical cancers now occur in the minority of women who are not adequately screened. Two-thirds of cervical cancers occur in women who have not been screened. Yet despite this enormous success, one third of preventable cervical cancer occur in women who have had a Pap smear in the last five years. Because cervical cancer is a slowly progressing cancer, often taking ten to fifteen years to develop, regular pap smear screening combined with new and cutting edge screening tools can lead to greater success in prevention. The success of cervical screening is that it detects abnormal cells which can be treated before cancer even develops.

CERVICAL CANCER AND THE HUMAN PAPILLOMAVIRUS (HPV)

Recent clinical studies have confirmed that the human papillomavirus (HPV) is the primary cause of cervical cancer. HPV is a very common virus which can infect anyone who has ever had sexual intercourse. In most cases, HPV is harmless and people never realize they have it. It is established that up to 80 percent of women in the United States contract the virus at some point during their lives. But, only a few of the women with HPV will develop cervical cancer. Although infection with certain types of HPV increases the risk of cervical cancer, most infected women do not develop cancer. In fact, of the more the 70 types of HPV, only 13 are associated with cervical cancer. The ability to identify the presence of high risk HPV may be the key in our efforts to combat this disease. Unfortunately, a recent survey confirmed that 70 percent of women are unable to name the cause of cervical cancer. While women should receive regular pap smear screening, in many cases, these screenings produce borderline results. Of the 50 million Pap smears performed in the United States annually, 3.5 million produce abnormal results. Recent studies have shown that as a follow-up to borderline pap smear results, the use of enhanced screening technologies, including a new test that detects the presence or absence of HPV, can give a woman's healthcare provider added information about the cause of her borderline results. Follow-up options can then be tailored appropriately.

AMWA'S PERSPECTIVE ON CERVICAL CANCER

AMWA believes cervical cancer can be the first major victory in the war against cancer. We believe that in order to achieve this victory, American women and their healthcare providers need more education about cervical cancer, the importance of regular pap smear screening, enhanced screening technologies, and current and cutting edge tests for the causes of cervical cancer. As an organization of women physicians, AMWA recognizes the crucial role we play in leading the fight against this cancer. We are more likely to provide pap smear screening, inform their patients about cervical cancer, and encourage routine screening. Essentially, the battle against cervical cancer can only be won with the two-fold strategy of increasing the number of well-educated, proactive women consumers and enlisting the help of physicians who encourage routine screening. AMWA views regular pap smear screening as critical in detecting cervical cancer. We also regard HPV testing, in the event of a borderline pap smear result, to be an effective way to provide healthcare providers with important additional information. To this end, we have become the lead partner in the National Cervical Cancer Public Education Campaign. The Campaign is a collaborative, educational effort involving representatives from leading women's health and civic organizations designed to inform women about the link between HPV and cervical cancer, reinforce the importance of regular pap smear screening, introduce new and existing methods to detect cervical cancer, and empower them to take an active role in discussing the disease with their healthcare providers. The goal of the Campaign is to reduce the number of preventable deaths caused each year by cervical cancer through increased education and outreach.

CONCLUSION

AMWA calls on Members of Congress to demonstrate their support for public education about cervical cancer by signing on as cosponsors of the Cervical Cancer Awareness Resolution that has been introduced by Representatives Millender-McDonald, Lazio and Coburn. The key to winning the fight against cervical cancer is early detection. We can screen for it, we can test for HPV, and we can treat it. No woman in this country need die from cervical cancer. If we all do our part, we can make this a reality.

Mr. COBURN. Thank you, Dr. Lenhart.

Ms. Gatscha, please.

STATEMENT OF ROSEMARIE GATSCHA

Ms. GATSCHA. Mr. Chairman, members of the subcommittee, on behalf of the American Society of Clinical Pathologists, I would like to thank you for inviting me to speak here today. My name is Rosemarie Gatscha, and I am the Cytology Manager at Memorial Sloan Kettering Cancer Center in New York City. I am here representing the ASCP, which is the largest medical laboratory organization in the world. ASCP represents 75,000 members, including board-certified pathologists, clinical scientists, and certified technologists and technicians.

I would like to take a moment to explain what I do as a cyto-technologist. Cells are collected from a woman's uterine cervix, placed on a smear, sent to the laboratory for processing and evaluation. Part of my job is processing. Most of my job is evaluating these Pap smears.

As you can see here, this gives you an example of some cells that are present on a smear. These cells, in particular, are cancer cells from cervical cancer. It gives you a feeling for the numbers of cells that are present on this smear. It varies anywhere from 30,000 to 200,000 cells. It is important that a well-trained eye be reviewing these cells, and that is what a cyto-technologist does, discriminates between normal and abnormal cells.

While it is difficult to believe more women die of cervical cancer because they have never had a Pap smear or because they haven't had a Pap smear in the last 5 years than those that die of a false negative Pap smear, there are many reasons why some women do not have Pap smears and there are reasons why they are less available to some women. Let's look at availability first.

ASCP's Board of Registry, in conjunction with MORPACE International, based in Detroit, conducts the biennial wage and vacancy survey of 2,500 medical laboratory supervisors. The 1998 data was just made available, and the information regarding cyto-technologists is of particular concern. The current vacancy rate for cyto-technologists working at the staff level is 10.5 percent. This is a 3 percent increase over the 1996 rate, which was 7 percent. This is the first increase in the cyto-technologist staff level vacancy rate in the last 8 years. What is critical to note is that the vacancy rate in rural areas is 17.6 percent. While the overall vacancy rate for supervisors, cyto-technology supervisors, has decreased slightly over the past 2 years, the vacancy rate in small medium-sized cities is increasing. It is 20 percent.

These data show some cause for concern, and I realize that sometimes numbers of this type may be meaningless, but to put it in perspective, you may recall the nursing shortage crisis. At the height of their crisis, the shortage was 11.3 percent.

Cyto-technologists are highly skilled and trained individuals. Laboratories rely on certified cyto-technologists to evaluate Pap smears. With high vacancy rates, there is concern that some laboratories will not have the appropriate personnel available to evaluate those Pap smears. This leads me to a related issue.

Cyto-pathology smears are currently priced at $7.15 on the Medicare laboratory fee schedule. The actual cost of the conventional Pap smear is between $13 and $17. This price includes cyto-technologists' salaries, overhead costs, CLIA-mandated quality control, and laboratory supplies, and also supplies that are given to healthcare providers who obtain the Pap smear. The Medicare payment rate for Pap smears should increase significantly. This, in turn, will help to alleviate the personnel shortages that exist which are amongst our most serious concerns.

Despite increased publicity and a greater emphasis on cervical cancer screening, a lack of knowledge continues to be a barrier to women in obtaining a Pap smear. A woman is more likely to obtain a smear if symptoms are present and if there is social pressure on her to do so. Barriers to obtaining a smear also include fear and embarrassment, belief that Pap smears are unnecessary for older women, economic factors, and language and cultural barriers.

We look forward to continuing to work with you on the prevention of cervical cancer by increasing the availability of trained cyto-technologists, increasing Medicare reimbursement for Pap smear testing, and minimizing economic and cultural factors that stop women from having Pap smears. Thank you very much for your attention. If there are any questions, I would be pleased to answer them.

[The prepared statement of Rosemarie Gatscha follows:]

PREPARED STATEMENT OF ROSE MARIE GATSCHA, AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS

Chairman Bilirakis, members of the subcommittee, my name is Rose Marie Gatscha, SCT(ASCP). I am Cytology Manager at Memorial Sloan-Kettering Cancer Center in New York City. I am here today representing the American Society of Clinical Pathologists.

The American Society of Clinical Pathologists (ASCP) is a nonprofit medical specialty society organized for educational and scientific purposes. Its 75,000 members include board certified pathologists, other physicians, clinical scientists, and certified technologists and technicians. These professionals recognize the Society as the principal source of continuing education in pathology and as the leading organization for the certification of laboratory personnel. ASCP's certifying board registers more than 150,000 laboratory professionals annually.

THE PAP SMEAR FACTS

The Pap smear is a proven screening method of detecting and preventing cervical cancer. It is the most effective cancer screening test in medical history as it is largely responsible for the 70% to 80% decline in death due to cervical cancer over the last 50 years in the United States.

Approximately 4,900 women die from cervical cancer annually in this country, making it the tenth leading cause of death from cancer in women. Approximately 14,000 new cases of cervical cancer are diagnosed each year.

The Pap smear is a safe, noninvasive, cost-effective medical procedure. Cells collected from a woman's uterine cervix are sent to a cytopathology laboratory where the cells are evaluated. The cytotechnologist prepares the slide and evaluates the specimen, which is composed of thousands of cells—usually between 30,000 to 200,000 cells in a single specimen. If the specimen is within normal limits, a report is sent to the woman's health care provider. If an abnormality is detected, then a pathologist examines the slide and issues a final diagnosis.

BARRIERS TO PAP SMEAR TESTING

While it is difficult to believe, more women (80%) die of cervical cancer because they have never had a Pap smear or they have not had a Pap smear in the last five years than those that die of a false negative Pap smear. We believe this is unconscionable.

There are many reasons why some women do not have Pap smears, or why Pap smears may be less available to women. I'd like to devote the rest of my comments to exploring those reasons.

Trained Cytotechnologists Are Needed

The American Society of Clinical Pathologists' Board of Registry, in conjunction with MORPACE International, Detroit, conducts a biennial wage and vacancy survey of 2,500 medical laboratory managers. The survey measures the vacancy rates for 10 medical laboratory positions, and compares and contrasts these data with that from 1988, 1990, 1992, 1994, and 1996 studies. The 1998 data has just been made available, and the information regarding cytotechnologists, the professionals who interpret cellular material such as Pap smears, is of particular interest and concern.

The current vacancy rate for cytotechnologists (staff level) is 10.5%, an increase over the 1996 rate, which was 7.1%. This is the first increase in the cytotechnologist (staff level) vacancy rate in eight years. It is also important to note that for rural areas, the cytotechnologist (staff level) vacancy rate is 17.6%, and totals 9.7% for small-medium size cities and 12.1% in large cities. Also, while the vacancy rate for cytotechnologist (staff level) in large hospitals is 8.3%, the vacancy rate nearly doubles for hospitals with a 100-299 bed size—up to 15.8%. Hospitals with bed size of 300-499 reported vacancy rates for these professionals at 14.3%.

Laboratory managers were questioned about the difficulty they have in filling work shifts. 21% reported problems recruiting cytotechnologist (staff level) for day shifts, three times higher than the 8% reporting such difficulties in 1996.

While the overall vacancy rate for cytotechnologist (supervisor) has decreased over the past two years, 10% down from 12.5%, the vacancy rate in small-medium size cities for cytotechnologist (supervisor) is 20.0%. Vacancy rates for cytotechnologist (supervisor), while virtually non-existent in the east north central, west south central, and far west regions of the country, are explosive in the northeast (16.7%), south central atlantic (18.2%), and west north central (12.5%) parts of the nation.

These data show some cause for concern. Cytotechnologists are highly skilled and trained individuals, who must have at least a baccalaureate degree followed by a year of specialized training in cytology. Cytotechnologists must then take a rigorous national certifying examination, administered by the ASCP, in order to become certified. Laboratories rely on certified cytotechnologists to evaluate all Pap smears. With high vacancy rates, there is concern that some laboratories will not have the appropriate personnel available to evaluate Pap smears.

Medicare Reimbursement

Cytopathology smears are currently priced at $7.15 on the Medicare laboratory fee schedule. The actual cost of the conventional Pap smear (excluding new technology and the professional component for physicians) is in the range of $13 to $17. The cost of new liquid-based Pap testing is $28-$32. This price includes cytotechnologist salaries, overhead costs, CLIA-mandated quality control, laboratory supplies, and supplies given to healthcare providers who obtain the smear. The Medicare payment rate for Pap smears should increase significantly.

ASCP and other organizations are working with the Health Care Financing Administration to increase the Medicare payment rate for Pap smears. In addition, Representative Neil Abercrombie and Representative Mary Bono have recently sponsored legislation, HR 976, to increase the Medicare payment rate to $14.60. ASCP supports this effort to bring attention to the need for the Pap test and a more appropriate payment rate.

Liability

With annual screening, the chance of a woman developing cervical cancer can be reduced to less than 1%. Pap smears have an irreducible false negative rate (10%-40%) due to sampling errors on the part of health care providers and screening errors occurring in laboratories.

According to a March 1997 report in the *Archives of Pathology and Laboratory Medicine,* the continued availability of Pap cancer screening test is threatened by lawsuits because the legal system demands a zero error rate which is mathematically unachievable even in the most competent professional hands.

Socioeconomic Barriers

According to Healthy People 2000, the National Health Promotion and Disease Prevention Objectives, there are several key assumptions that may be used to help overcome barriers to cervical cancer screening. The objectives state, “low income, low education and advancing age are all associated with a decreased likelihood of receiving Pap tests.” The report continues that “age influences both cervical cancer incidence and survival. While younger women are more frequently diagnosed with cervical cancer, older women are more often diagnosed at later stages of the disease and are more likely to die from it than younger women.” We are also aware that certain populations of women—African American, Hispanic, Asian, and low-income rural women—often face cultural and economic barriers to Pap screening.

For example, it is not uncommon for low-income women of Hispanic descent to refuse Pap testing. Even if the Pap smear is free or of little cost, these women, whose families may rely on them for income and support, refuse the test because they do not want to know if they have cancer. A cancer diagnosis, in this instance, would mean extensive, and often prohibitive, medical costs to treat the cancer, and would tear the women away from their families for extended periods of time. Many women in this situation prefer not to know their potential cancer status. In addition, a lack of culturally appropriate materials or information communicated in Spanish is a barrier to Hispanic women being screened.

In a study compiled by the Centers for Disease and Prevention, it was determined that transportation and its costs were barriers to Pap testing for Native American women.

In speaking with public health officials, we are also aware of examples in certain Asian-American communities where it is considered shameful for women to have a Pap smear. In this culture, husbands may not want their wives to be examined “in that way” by a male physician.

SOLUTIONS

The Pap smear, named for its creator Dr. George N. Papanicolaou, is one of the most effective cancer screening tools available to women today. There are ways to lessen the barriers that exist to Pap testing, so that cervical cancer becomes a less formidable disease to women.

ASCP continues to work with the cytology community to provide continuing education and certification for these laboratory professionals. ASCP has also established a scholarship program for medical technology students, including cytotechnologists. The Society awards 100 student scholarships each year to assist with educational finances.

Last year, your Committee reauthorized Title VII of the Public Health Service Act (Health Professions Education Partnerships Act of 1998, P.L. 105-392), which included a program for Allied Health Project Grants. This program has been effective in addressing the training and educational needs of allied health personnel, including cytotechnologists. However, further strides in funding are still needed to increase the number of cytotechnologists to an adequate level.

Increasing the Medicare reimbursement for Pap testing to an amount more in line with current costs would also help to attract and retain professionals in the field.

ASCP, along with many other organizations, are working to educate the general public and the priority populations mentioned above about the importance and effectiveness of the Pap smear. We are particularly proud of the efforts we have undertaken to help educate other health care providers about the Pap smear.

ASCP believes it is important to develop and disseminate educational materials to targetted populations and to the health care providers that serve them, and develop relationships with community organizations, such as schools, retailers, employers, social facilities, and churches, to assist in reaching women that are not participating in cervical cancer screening programs.

We aim to continue these educational efforts, and look forward to working with you and others in the prevention of cervical cancer.

I would be pleased to answer any questions you may have.

Mr. COBURN. Thank you, Ms. Gatscha.

I am going to take the first round of questions, if I may. Dr. Cox, would you tell us a little more about the ALTS study and what you hope to come out of that, and the implications for us in terms of health policy?

Mr. COX. Yes, I would be very happy to. As you know, the 1988 Bethesda guidelines created a new category called ASCUS. And ASCUS, as an OB-GYN, you know has been probably the hardest Pap smear reading for us to deal with. That is why many people say, “Don’t ASCUS,” because it is an equivocal pap. The problem with it is that it is the most common Pap smear reading that is considered abnormal. It is the least risky in terms of the percentage of those with ASCUS that have high-grade disease. About 6 to 8 percent will have high grade disease. However, the total high-grade disease discovered by Pap smear in the United States, about 30 to 40 percent of it comes from ASCUS. A great deal of cancer comes from under that Pap smear reading as well. So, it is our biggest problem, because most people are normal, but there is this hidden sort of group underneath that are very, very risky.

So the ASCUS LSIL trial was set up to evaluate whether it is best to refer women immediately to colposcopy, which is looking at the cervix with a microscope on the stand in the doctor’s office, whether it is better to do that immediately, whether it is better to follow ASCUS by repeating the Pap 3 or 4 times, and if any repeat Pap is abnormal, then colposcopy in those women, and if they are not abnormal, sending them back to annual exams; or whether it is better to test for the causing by bringing the woman back in and doing an HPV test on followup; and colposcopy in those women high-risk positive and returning the women that are not a high-risk positive either to a Pap in 6 months and then annual exams, or maybe immediately to Pap smear annually. So the ASCUS LSIL trial was specifically set up to determine which triage is most cost-effective, which detects the most high-grade disease, which is most patient-acceptable, as a very extensive ongoing patient questionnaire to see what kinds of issues and anxieties are involved with each office visit, et cetera, so that we get some kind of an idea what women want to do the most.

Mr. COBURN. You mentioned, can you explain for the rest of the panel a little bit, about what the new thin-prep is and how it works and why it is reported to help us in terms of diagnostic criteria?

Mr. COX. In 1996, the FDA approved thin-prep paps, and they are, I believe, going to be soon approving a liquid-based Pap for Roche as well called CytoRich. These are Pap smears in which the sample is taken from the cervix in the same manner as for a glass slide pap, which is a conventional pap. But instead of putting the swab in, or with a collection device immediately on, a slide is put into a liquid media. In terms of the thin-prep pap, that liquid media is sent to the cyto-pathology laboratory. A cylinder is put in the liquid media and spun to disperse the cells. The cells are sucked into a filter, and when about 70,000 cells hits that filter enough, a vacuum pressure, the vacuum pressure device determines how many cells are there. It shuts the vacuum off, and then that little filter, 2-centimeter filter of cells is turned upside down on a slide, and a positive pressure puts the cells in the slide. What it does is it removes potentially obscuring materials, especially vaginal discharge. It disperses the cells on a slide in what is called a monolayer, so that the cells are not overlapping each other. So what it allows is for the slide to be looked at by the cyto-tech without having the potential of inability to see individual cells.

I should actually have, Ms. Gatscha, or a——

Ms. GATSCHA. Yes.

Mr. COX. There you are. I couldn't see you there for a minute. Basically, that would be something for you to comment on as well.

So that is a thin-prep process, and it has been evaluated in the ALTS trial as well as HPV testing.

Mr. COBURN. Okay, there's just one followup. Could you let the panel know that the difference is in cost in your area for a thin-prep versus a conventional pap?

Mr. COX. Right. Well, my wife had one recently and it was $60. I don't know; I think the lab charges for—this is private paid—the lab charges $32 or $34 for conventional pap. For the health center, I can say that the conventional Pap is $10. The thin-prep Pap is $20. Basically, the thin-prep Pap has a set incremental fee that has to be attached until the prices come down, and that is that it is $9.75 for the materials that are disposable in the pap, because of the filter, the liquid media, and some element of usage of the thin-prep machine which cost in itself for the lab to get.

Mr. COBURN. The gentleman from Ohio.

Mr. BROWN. Thank you, Mr. Chairman.

I think you heard, I think all three of you were sitting there patiently during the last panel, and I had a discussion with Dr. Lee about MQSA, what Congress did with that and with licensing and inspection of mammography facilities, and how that, I think, has been a true success across the country. Could you comment, I suppose especially Ms. Gatscha, but really all three of you, on any thoughts you would have with—obviously, with mammography facilities there is not the problem, as Dr. Lee said, as with Pap smears of 50 percent of errors due to healthcare provider errors, 50 percent lab errors. I mean, it is obviously a different phenomenon with MQSA and with mammography facilities.

But could you run through what might make the most sense in terms of better national licensing or annual inspections or licensing and training of personnel or what we might want to do?

Ms. GATSCHA. Yes. What I have found to be the most remarkable thing that has happened is CLIA-88. Many laboratories that were called into question in all of these articles that we read in The Wall Street Journal, et cetera, have been forced to institute quality assurance programs. And that, in my estimation, has been the strongest avenue to pulling the test results into place—getting more accurate results, results that correlate with surgical pathology. I think that has been the strongest impetus.

Mr. BROWN. Dr. Lenhart, do you have any thoughts on it?

Mr. LENHART. Well, I think you have to take into consideration more that we are just beginning to regulate those who read the slides. Because some of the newer techniques involve less and less technology from the individual pathologists. The auto-prep and papnet involve computerized technologies. So that if you were only to look at making sure that—it is not really analogous to mammography. That is why we are proposing that the public as well as healthcare providers start thinking about the best way to use these enhanced technologies. Because they might eliminate some of those errors through the enhanced technologies without the regulation. They also might allow for screening to occur less frequently. They also might make it clear to those women who are dealing with borderline paps who is really at risk and who isn't, which would eliminate a lot of anxiety. So we see it as more complicated than just looking at how to make sure that those who read Pap smears do it consistently and well.

Mr. COBURN. Would the gentlemen yield for just a second?

Have there not been a couple of studies that have already showed those advanced technologies as improving our diagnostic skills at a lower cost?

Mr. LENHART. Yes.

Mr. COX. You know, I think enhancing regulation will not be very helpful. I think it is clear CLIA-88 has had a major impact on lab quality in almost every area except Pap smear. There have been several good studies on the 10 percent rescreening, and it has shown that really the amount of disease picked up by 10 percent rescreen is very, very little. I think that if we are going to really look at how to make the system work better, we have to realize that a false negative pap, only about 30 percent are screening or interpretive errors. There is the other 70 percent that are sampling or preparation errors or cells just not on the slide, for whatever reason. And if we are going to make a major impact in this problem, we need to try to improve the Pap upfront, if that is possible.

Now, I think the thin-layer cytology does improve the Pap smear upfront, but on a year-to-year, on an annual basis of using it annually, it probably is not cost-effective, unless we are willing to put that extra money into it and just say it is a better test and that we are willing to fund it. But if we really look at the ability of a better Pap to potentially allow us to increase the screening interval, and realizing that many people have an increased screening interval anyway—many people only go in every two or 3 years. So if we have a better Pap applied to that, then in the end, we don't have to do paps every year, that would save substantial money down the road.

Part of the reason it would save substantial money is that you have to remember that 5 to 10 percent of women that go in and get paps every year on an annual basis will get either an equivocal Pap or a Pap that is limited in quality; both of those require a physician response, bringing the patient back for some response. So, those are in many instances false positives. If we don't have to do that on a yearly basis and bring all of those in, but only have that risk, say, every 3 years, our system will get much more cost-efficient than it is right now, and we can still, I think, pick up as much or more cancer than we are picking up under the present system.

Mr. COBURN. The gentlelady from California.

Mrs. CAPPS. Thank you. I want to acknowledge—first of all, thank you for your testimony, and I would like to address it briefly. I know the hour is getting late, but we have sitting through this whole discussion this afternoon Dr. Wanda Jones, from the Women's Health Office, Department of Health and Human Services. I think that is a credit to what they are doing in their office and also bears a lot on what we are talking about today.

It calls to mind for me the United States Public Health Service, in combination with the Department of Defense, this wonderful mobile unit for a mammogram, the state-of-the-art that I was able to, when I was a congressional spouse, had a tour of. There are innovations happening in cancer detection here, in our Nation's Capital, but also all throughout the country. That is what I find intriguing about it.

So I want to commend the efforts of the Women's Health office for what you do, and also the three of you are touching on—and I know that it must be frustrating for you because we are barely getting into the topics that you care so deeply about. But that is the nature of what we do here. And right now, at this late hour, we are getting to part of the discussion that we could really sink our teeth into and say, you know, what is the next thing to do?

Here I feel such an dichotomy. We have a treatable disease, and I have had a personal experience now. My daughter was just diagnosed with cancer, not this kind, within the last month. So I am entered into a world that I didn't think I would have to learn about this way.

But here we have a preventable disease, according to a screening device, which is fairly routine, and I hear from you, Ms. Gatscha, the reimbursement rate has something to do with how effective this is going to be and we need to be addressing that here on the Hill. Also, we have the challenge of getting this screening out to more women and having them know more about—well, not just women, our society in general. I don't want to pin it all onto women—to know what to do about our bodies and how to prevent preventable diseases. So we don't want to lose that track.

Yet, you are saying we should be going the next step. We shouldn't be content with the Pap smear that was around 50—I know it has been improved, but maybe there is different concepts.

So, with the little tiny bit of time, can you tell me how we should proceed here on the Hill with this topic now? And thank you.

Mr. COX. Where I have a hard time answering that is I am not sure what laws or power you have in terms of making changes in this. My personal feeling is that the agencies that have been set up to explore cost-effectiveness and cervical cancer screening have taken only a single end-point and used a model that was made in 1985 or made in 1990, but used 1985, International Agency for Research on Cancer data. The model uses a $3 cost for Pap smears. It uses a false negative rate of Pap smears of 2 to 3 percent. It uses as the only end-point years of life saved, which if you divide the number of lives lost in the United States per year by 50 million women screened, comes out to very small numbers, especially when you talk about enhancements that might improve that.

So, what I would really like to see you all encourage is that, in those situations in which there are official assessments of cost-effectiveness, that really we take into account cost-benefit analysis and quality-of-life years. Because those are what really matter to women. Women are not at huge risk over their lifetime of dying of cervical cancer, but they are at huge risk of getting anxiety and distress over being diagnosed with something that may have little adverse effect on them either now or in the immediate future.

I think that we can utilize cost-benefit analysis in a way in which we can find that this system can be organized in a much better way than it is, and that it can be still as effective, and probably more so, with not nearly so much trauma, both physical and psychological, to women.

So that is where I would like to take it. I would also mention maybe not starting the screening interval at 18, and I figured I'd get some real hackles out of people for that. I am basically in a center where I see 18- to 22-year-olds, and I have never seen a cancer in this age group, not an epithelial cancer. I've seen rabdomile sarcomas, et cetera, but not epithelial cancers. And, indeed, epithelial cancers are extremely uncommon in women under the age of 24.

So I think that we could consider, if we have to save money in the screening system to put elsewhere, to higher-risk groups, et cetera—maybe we don't—but if we do, I think we could consider looking at what the rest of the world does and make that screening start a little bit later, especially in terms of the trauma that occurs with young people considering the very high positive rate of HPV in that group, the very high positive transient nature of the HPV effect in that age group.

Mrs. CAPPS. Thank you. More flexibility then, or——

Mr. LENHART. I would like to add two thoughts that we learned through the AMWA campaign that might be utilized on a more Federal basis. The first is the importance of involving multi-specialty groups in formulating policy. Our advisory committee not only included pathologists, cytologists, and some experts in virology, but also practicing clinicians, both primary care physicians, obstetrician, gynecologists. It was a very variable group. And if you want to really tease out cost-effectiveness, and the complexity of the issue, you want to develop policy based on a consensus group that is more variable than is often involved.

The second thing that we learned was not to underestimate the low cost in high efficiency of women's capacity to be pro-active and to communicate. The cost of our campaign is relatively low because, essentially, we took our multi-specialty advisory committee, said, what are the key things that women should know that they don't know about both what's new and about what they should be doing more of? Then we gave that information free of charge to a number of women's organizations, many of them minority organizations, and said to them, "This is what is important. You figure it out." We gave them suggestions. "But you figure out the best way to get this information across to your groups." That is pretty cheap.

Mr. COBURN. Dr. Lenhart, let me interrupt and give Mr. Towns his time, if we may. We are running way over, and many of us have to be in other places about 10 minutes ago. The gentleman from New York.

Mr. TOWNS. I will definitely try to respect that, Mr. Chairman, and be as brief as possible.

You know, I guess I want to ask each panelist this. In your opinion, what is the greatest constraint for women to get access to quality Pap smears? What is the greatest constraint?

Mr. COX. There is a whole slew of studies and literature on this right now. And, unfortunately, they are not going to help answer that question very much because most of them have indicated the cost is not the primary issue. And, in fact, you can look at the Kaiser system, and you can look at the Canadian system, where cost is not a factor—women get free access to Pap smears—and, yet, this same percentage of women that get cervical cancer in that system are those women that don't get screened. So, it is not, it doesn't appear to be a cost issue.

There really are societal, cultural issues, especially cultural, that we have a harder time penetrating, and especially in our wonderfully diverse society we have so many cultures come in, in which really something that is in that part of the human anatomy is really not something that is shown even for exam. And, it is those kinds of issues that we have a hard time getting beyond. If we can find ways to overcome the cultural and societal issues, then I think that we may be able to get many, many of these women in. But that is the hardest thing to crack, I believe.

Mr. TOWNS. Let me ask you, Doctor, if they come in—I am not sure that I am hearing that the medical staff encourages them, even when they come in. Then when they come in for something else, do they actually encourage them to take a Pap smear? Is that going on? I get the feeling that there is something missing here.

Mr. COX. I agree. I think that what you are alluding to is that there are often visits to the medical practitioner by patients, by women, who have never had a Pap or have not had one in many, many years, and they are there for some other reason and the Pap smear is not done. And I think that is one of the things that we have to do. We have to educate physicians to always be wary of the fact that when a woman comes in, a Pap needs to be done.

Kaiser published a good study in the Green Journal this year in which they showed that 60 percent of the cancers in their population were in women that had not had a Pap smear or not had one in the last 5 years, and the majority of those women had been in the Kaiser system for some other reason and had just not had a Pap when they were there. This is a real tragedy and something that has got to be corrected.

Mr. LENHART. We would agree with that. We think that a lot of the new information, as well as a lot of vital women's health information in general, is often missed in the doctor's office. So we have sponsored a number of physician education programs that are targeted at getting the information out, as well as converting the doctors into advocates and better communicators, but also patients into advocates and better communicators with their physicians. We think that dialog is a very important one to monitor.

Mr. TOWNS. Do you want to add to this?

Ms. GATSCHA. Yes, well, just one thing really, because those are the cruxes of this matter. But I think, also, this information has to be disseminated at other levels because there are lots of people who don't go to a doctor. They are just well. They don't go and no one says, "Hey, have you had a Pap smear?" I think that at the community level, churches, schools, this information has to be part of health programs in elementary and high schools. Hopefully, by college, when many young women do become sexually active, then they will have these tools to use to help them prevent this disease.

Mr. TOWNS. Thank you. Just one other question which is sort of really bothering me: Is it realistic to expect that women, and particularly low-income women, will have access to new cervical cancer treatment? Is it realistic to think that they will.?

Mr. COX. Well, I think that resources are available in most States. I can only answer for my State—that that there are resources for almost all women to get Pap smear screening. There is Medical/Medicaid. There is State Office of Family Planning, which provides Pap smears to women coming in for family planning. I think that it is uncommon in the State of California for there to be women totally outside the system, unaffordable. Even for women that are caught between the really low-income level and the job level where they have insurance coverage, there are some women that are not rich and not poor and don't have insurance. Those are the ones that often have the hardest time, but paps are available through Planned Parenthood, for instance, and other agencies on a sliding scale that can be very helpful for those women.

I think one of the things we forget is that Planned Parenthood provides about 2.5 million paps in the United States per year. It provides more paps than any other organization in the United States, and so that is a very important function for it, that women that might otherwise slip through the cracks would have access to.

Mr. COBURN. Would the gentleman yield?

Dr. Lee did testify—she was asked that specific question by Ms. Eshoo, and her response was, they are getting the care, you know, which surprised me. I will just admit to you I was surprised at her answer, and I am going to ask her for that data, which leads me to the next question.

I would like unanimous consent to add to the record and leave the record open until the questions are formulated for our panel.

Other then that, I want to thank each of you for being here and for your contribution and your time.

Mr. COX. Thank you very much.

Mr. COBURN. The meeting is adjourned. I guess you do this: [using gavel].

[Whereupon, at 5:45 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

PREPARED STATEMENT OF CAROL ANN ARMENTI, DIRECTOR, CENTER FOR CERVICAL HEALTH

It is my privilege to contribute to these proceedings on cervical issues as a cervical cancer survivor, a patient advocate and a healthcare professional. In a recent media interview I was asked with how many women did the *Center for Cervical Health* have direct contact over the past year. I was surprised to find that our website, which we are proud to say has been reviewed, approved by and linked to such prestigious organizations as Yale University, the Women's Cancer Network, and the Society of Gynecological Oncology, receives several thousand accesses a week, and that I personally counsel and refer for treatment as many as a dozen women in a week.

It has been my distinct pleasure and honor this past year to be the first patient advocate appointed to the American Medical Association National Patient Safety Council, to serve as the New Jersey State Cervical Chair of the Center for Disease Control Breast and Cervical Program, and to be cervical cancer survivor representative to the National Cancer Institute Survivorship Research Conference. I served on the National Institute of Health cancer survivorship grant funding panel which—for the first time—permitted advocates a full vote on funding proposals. It was a similar honor to testify before the Food and Drug Administration, this past year, on new technologies in the detection of cervical disease.

I am blessed with the support of the print and broadcasting media, advocacy organizations, medical groups and private industry. But I am most blessed with this opportunity to represent to you the courage of those suffering from cervical disease in this country, it is with frustration and anger on their behalf that I advise you of their unmet needs, and it is with hope that I ask for the increased support they deserve.

I call to your attention that fourteen per cent of *all* cancer survivors are those surviving cervical cancer. Other than breast cancer, it arguably represents the largest group surviving any form of cancer in this country yet relatively little is done to support these women who have had what is unique to their being, their reproductive organs, mutilated and destroyed. This past week at a National Cancer Institute Survivorship Research Conference *not one* research project which focused on cervical cancer was presented in two days of lecture.

Of the nearly eighty grant proposals on cancer survivorship submitted to the National Institute of Health *not one*—other than a DES follow-up study—focused on cervical cancer. Indeed, I was recently contacted by a cancer center in Colorado which was attempting a study on cervical cancer survivors. The researchers were disconcerted because they could not find more than two dozen cancer survivors eligible and willing to participate in a study. I immediately contacted two prominent cancer advocates whom I know to be surviving cervical cancer and I was told that they did not wish to become "public."

Our society has branded these women pariahs. They are ashamed to discuss their disease, and even worse, they are so embarrassed to discuss their symptoms that they frequently do not seek detection of early precursor conditions or obtain effective treatment of disease. It is incumbent upon us as a nation to provide women with the education they need in their earliest, as well as their latest, years to protect their lives and their reproductive system. It is further incumbent upon us as a nation to provide adequate funding and assurances that women who seek detection and treatment will receive it.

Strides are currently being made in the areas of detection, new technologies which may prove successful in determining the genesis of disease. New treatments and vaccines are showing great promise for the reduction in morbidity and mortality of cervical disease. Yet I see little improvement in the education of young women which may help them make better choices. We must see programs which will inform all women on the damage to their reproductive systems caused by smoking, and inform young women especially of the increased risk to which they expose themselves by relations in their teenage years when their immune systems may be especially unable to fight disease.

Similarly, I see little in this country done to educate physicians to the symptoms of cervical disease and even less done to inform them on new methods of detection and treatment.

Nearly two years ago because of the great silent suffering of these women who were willing to share their experiences with me both as a sister survivor and psychologist, I began my efforts to increase public awareness. Part of those efforts resulted in the declaration of January as Cervical Health Month by this administration. Our reward was dozens of programs across the country encouraging women to protect themselves by having Pap tests, the single most successful cancer screening device ever devised, and to have pelvic examinations. Part of our efforts is the Resolution, consistent with its predecessor sister resolution for breast cancer survivors, currently before the Senate declaring Cervical Health Month and conveying the sense of the Senate that these women and their families deserve support.

I further ask this Committee to support increased funding programs for the detection of cervical disease. It is oftentimes said that fully half of the women who develop cervical cancer did not receive a Pap test. This statement is made as an indictment of those women who develop the disease as if they were somehow responsible for their own illness. In the State of New Jersey we are both proud and saddened to say that we gave a party and everyone came. That is, not only did we achieve our goals in the numbers of women who responded to our CDC underserved program, more women came than we had funds to test. We must ensure that all women who wish to be tested, are tested.

I ask that this Committee encourage studies which will ease the burden of those surviving cervical cancer. We can learn from these women how best to treat future disease with less destruction and less mortality. I call to your attention that while the death rate of other cancers has declined, the mortality rate of cervical cancer is expected to *increase* this year.

Finally, I ask that you encourage the education of both women and physicians on causes, symptoms and treatments of this disease, and that we do so without the moral judgment which has made women too ashamed in the past to seek detection and treatment.

I once again thank you for this opportunity to address this Committee.

DEPARTMENT OF HEALTH & HUMAN SERVICES
NATIONAL CANCER INSTITUTE
April 8, 1999

The Honorable MICHAEL BILIRAKIS
Chairman, Subcommittee on Health and Environment
Committee on Commerce
House of Representatives
Washington, D.C. 20515

DEAR MR. CHAIRMAN: I am responding to your letter of March 19, 1999, in which you pose five questions as a follow-up to my testimony before the Subcommittee on Health and Environment on March 16, 1999.

As requested, the questions have been restated below. The answer follows each numbered question.

Question 1. What are some of the side effects of various forms of cervical cancer treatment?

Response. Three kinds of treatments are used for cervical cancer: surgery, radiation therapy and chemotherapy and side effects vary depending on the type of treatment chosen. There are also several different types of surgery that are used to treat cervical cancer. The stage of cervical cancer at the time of diagnosis determines the type of treatment and will determine possible side effects.

Methods for removing or destroying small cancers on the surface of the cervix include: cryosurgery which kills the cancer by freezing; cauterization (burning) or laser surgery which destroys the abnormal area without harming nearby healthy tissue; a loop electrosurgical excision procedure (LEEP) may be preformed in which an electrical current is passed through a thin wire loop that acts as a knife to remove the abnormal tissue; and conization in which a cone-shaped piece of tissue is removed where the abnormality is found. These treatments may cause cramping or other pain, bleeding, or a watery discharge.

Hysterectomy is another surgical procedure used in the treatment of advanced cervical cancer. Women who have a hysterectomy may experience pain in the lower abdomen for a few days following surgery. They will no longer have their menstrual periods and can no longer have children. Sexual dysfunction is another possible side effect. Women who undergo hysterectomy also face the risks of major surgery, including bleeding, infection, and damage to other organs.

Side effects of radiation treatment can include infertility, sexual dysfunction, fatigue, hair loss, skin conditions, diarrhea, and frequent and uncomfortable urination.

Side effects of chemotherapy depend on the drugs and doses the patient receives. Side effects can include increased susceptibility to infections, bruising, low energy, hair loss, poor appetite, vomiting, and mouth sores. Side effects gradually go away during the recovery periods between treatments. Women treated with cisplatin can also develop chronic neuropathy and renal damage.

Question 2. How can screening methods for cervical cancer be improved?

Response. The Pap test is currently the accepted method used to screen for cervical cancer and has been very successful in reducing the death rate from cervical cancer. However, as with any medical test, the Pap smear has limitations, particularly with respect to false-negative screening results. Recently, interest has focused on development of technologies to enhance the accuracy of cervical cancer screening. Some of these techniques are directed at improving the sampling and specimen quality, others are focused on improving the laboratory microscopic screening process, and some techniques are visual or molecular rather than microscopic.

Methods to improve sampling and specimen quality include the use of liquid-based collection techniques. Liquid-based collections offer improved fixation and presentation of the material in a more uniform manner than traditional smears which could make detection of abnormal cells easier. This technique also has the ability to test for HPV infection if there is a low-grade or equivocal cytology result which eliminates additional patient visits for testing.

Computer image analysis has been approved to screen cervical cytology specimens in an effort to reduce false-negative results. While this technology increases the screening sensitivity for atypical squamous cells of undetermined significance and low grade squamous intraepithelial lesion diagnosis it comes at a significant cost. Used in a secondary screening mode, these technologies are cost-effective only if incorporated into a less frequent screening strategy.

Question 3. What type of education campaign has the National Cancer Institute (NCI) sponsored to increase the awareness of cervical cancer? Please be specific in describing how NCI has coordinated its activities with other Federal agencies and programs.

Response. Federal agencies are designated to serve the United States in specific ways. The National Institutes of Health (NIH), of which NCI is a part, is a research agency. In its mission to protect and improve human health, the NIH (and NCI) conducts and supports basic, applied, and clinical and health services research to understand the processes underlying human health and to acquire new knowledge to help prevent, diagnose, and treat human disease and disabilities. This may include developing an information campaign such as the *Pap Tests: A healthy habit for life* campaign and evaluating its effectiveness at achieving its goal. NCI also has a mandate to disseminate research findings so that when the development and evaluation are completed, other Federal and state agencies, and private sector organizations, may take this information and apply it accordingly. NCI, therefore, plays an integral role in these activities.

The NCI disseminates research findings widely through scientific publication, press conferences, press statements, clinical alerts, patient education materials, meetings of professional societies, television and radio, the World Wide Web, our toll-free Cancer Information Service, our PDQ databases, and the Information Associates Program. Our staff has many contacts within agencies for a variety of programs and issues. Through these personal contacts, and those mechanisms mentioned above, Federal agencies and offices have direct access to information pertinent to their programs. In addition, we maintain and foster close working relationships with other Institutes that have formal collaborative relationships with the Office os Population Affairs-our projects and programs are thus included in that broad knowledge base. NCI has several partnerships with other federal agencies and non-federal groups to enhance our information dissemination activities The following are examples of two specific information campaigns on cervical cancer:

Pap Tests: A healthy habit for life: In May 1998 the Office of Cancer Communications began a campaign to alert the public of the results of a survey that showed that older women were unaware of their continued risk for cervical cancer. National activities have included the distribution of a media packet that focused on cervical cancer and older women. Additionally, NCI collaborated with the Health Care Financing Administration (HCFA) to reprint an NCI cervical cancer publication with Medicare information for older women. Other activities have included conducting research with physicians to identify their attitudes and perceptions of Pap test screening among women 65 and older. Based on this research, a print public service announcement and newsletter article are being developed that encourage physicians to talk to their older patients about Pap test screening. These materials will be promoted through physician publications and newsletters.

The Pap Test and Cervical Cancer Video: An intertribal video on the early detection of cervical cancer for American Indian women was produced by the NCI in conjunction with the Nebraska Department of Health. The video comes with educational material to help inform American Indian women of the importance of regular Pap tests.

Question 4. What is being done to improve the quality of life for women who are diagnosed and treated for cervical cancer?

Response. Improving the quality of life for cancer patients is a very important part of research at NCI. Currently, NCI is working to evaluate interventions which can reduce sexual dysfunction caused by radiation therapy. In addition, the NCI has ongoing research on ways to reduce damage to normal tissue from radiation therapy. The NCI also has plans to study fertility-sparing surgery for women with early stage cervical cancer.

Question 5. In your testimony, you discussed clinical trials that NCI is conducting on cervical cancer. What is the percentage of cervical cancer patients who participate in these trials?

Response. Approximately 2-3% of women diagnosed with cervical cancer are enrolled on cancer treatment trials sponsored by the NCI. This figure is consistent with other adult cancer sites.

Please do not hesitate to contact me if you have further questions.

Sincerely,

EDWARD L. TRIMBLE, M.D.
Head Surgery Section, Division of Cancer Treatment and Diagnosis

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DEPARTMENT OF HEALTH & HUMAN SERVICES
NATIONAL CANCER INSTITUTE
April 8, 1999

The Honorable MICHAEL BILIRAKIS
Chairman, Subcommittee on Health and Environment
Committee on Commerce
House of Representatives
Washington, D.C. 20515

DEAR MR. CHAIRMAN: I am responding to your letter of March 19, 1999, in which you pose twelve questions as a follow-up to my testimony before the Subcommittee on Health and Environment on March 16, 1999.

As requested, the questions have been restated below. The answer follows each numbered question.

Question 1. The National Cancer Institute (NCI) is in the process of conducting a randomized trial to establish the best way to manage abnormalities that are discovered during Pap smear tests. This study is often referred to as ASCUS/LSIL Triage Study or ALTS. Please explain the purpose and significance of this trial?

Response. NCI is conducting a large randomized trial to find the best way to manage the mild abnormalities that often show up on Pap tests and may, in rare instances, progress to cancer if left untreated. The ALTS trial is comparing three approaches: 1) immediate colposcopy (a procedure in which a physician examines the cervix through a magnifying instrument and biopsies any abnormal area; 2) repeating the Pap test every six months (because most abnormalities return to normal without treatment); and 3) testing for cancer-associated types of HPV as a means to differentiate between abnormalities that need immediate colposcopy and those that can be best followed with repeat Pap tests. Researchers will compare the three different groups to assess the effectiveness of each management option in detecting the serious abnormalities that can progress to cancer, the acceptability of each option to patients, and the cost effectiveness of each option.

Question 2. When do you estimate the NCI will develop a vaccine for human papillomavirus (HPV)? Can you describe all of the different HPV vaccines that are being tested?

Response. There are both preventative and therapeutic HPV vaccines which have been developed by the NCI that are currently being tested in clinical trials. They seek to prevent infection or to induce regression of established infection via immune recognition of specific HPV-encoded proteins or peptides. Such vaccines can be delivered either directly as a protein or by viral vectors derived from organisms of a different but related species.

Question 3. What effect, if any, does HPV have on men?

Response. Scientists have found an association between several types of HPV and the development of anal cancer and cancer of the penis (a rare cancer). HPV also frequently causes benign warts.

Question 4. In addition to cervical cancer, what other effects can HPV have on the body?

Response. Genital warts (condylomata acuminata or venereal warts) are caused by only a few of the many types of HPV. Other common types of HPV infections, such as those that cause warts on the hands and soles of the feet, only rarely cause genital warts. In women, the warts occur on the outside and inside of the vagina, on the cervix, or around the anus. In men, genital warts are less common. If present, they are seen on the tip of the penis or the urethra; however, they also may be found on the shaft of the penis, on the scrotum, or around the anus. Rarely, genital warts also can develop in the mouth or throat of a person who has had oral sexual contact with an infected person.

Question 5. Please provide the number of HPV cases in the U.S. Is this number increasing or decreasing? To what can this trend be attributed?

Response. It is important to remember that estimating the prevalence of HPV is difficult. Prevalence depends on many factors which include: the population screened, the sexual habits of those screened, what is classified as HPV infection at the time of screening, etc. Estimates for the number of HPV cases varies. In November of 1996 the CDC estimated that 24 million Americans were infected with HPV. The incidence of HPV infection has increased with changing sexual mores starting in the 1960's. It is difficult to know whether variations in incidence and prevalence reported during the 1990's represent an actual change in the number of cases of HPV.

Question 6. What, if any symptoms are associated with HPV? If it is asymptomatic, how would one know one is infected?

Response. HPV may cause warts with many different characteristics. They may appear small or large, flat or raised, single or multiple; sometimes the warts may not even be visible to the naked eye. The most common places to notice genital warts are outside the vagina, on the penis, and around the anus. In women, HPV can lead to the development of warts inside the vagina and on the cervix as well. For many people who have HPV infection, there are no obvious signs of infection. However, if warts are present, a doctor can diagnose HPV infection by their characteristic appearance and the history of how they developed. In women, to look for warts on the cervix or in the vagina, a doctor may use a colposcope, which is like a telescope. In addition, Pap smear results may be suggestive of HPV infection. There is currently no blood test that has proven reliable in the diagnosis of HPV infection and it is not possible to routinely culture HPV. However, there are sensitive DNA based assays which can be used to diagnose symptomatic and asymptomatic HPV infection.

Question 7. How widespread or common is HPV? Of the women who have HPV, what is the percentage of those women who will develop cervical cancer?

Response. More than 80 types of HPV have been identified. However, approximately 25 types infect the uterine cervix; of these, only some are associated with invasive cervical cancer. They are therefore classified into low-risk types, HPV 6 and 11, and high-risk types, most commonly 16, 18, 31, and 45, which account for more than 80 percent of all invasive cervical cancers. Less than 15 percent of women infected with HPV will develop either low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL). At least one-third of all grades of SIL will fade, whereas less than half persist and approximately one-quarter progress. Of lesions that progress, approximately 10 percent progress to carcinoma in situ and 1 percent to invasive cancer.

Since the virus is transmitted primarily through sexual intercourse, there seems to be a peak prevalence of infection in sexually active women who are younger than 25 years of age. The prevalence of infection decreases with increasing age, suggesting that most infections in women and men resolve over time through host immune responses.

Question 8. The NCI has identified risk factors, such as the human papillomavirus, in the development of cervical cancer. What work has NCI done to coordinate a Federal response to the prevention of cervical cancer? Specifically, what has NCI done to coordinate with the Department of Health and Human Services (HHS) Office of Population Affairs and the HHS Health Resources and Services Administration (HRSA) to alert women concerning the risk factors associated with cervical cancer?

Response. Federal agencies are designated to serve the United States in specific ways. The National Institutes of Health (NIH), of which NCI is a part, is a research agency. In its mission to protect and improve human health, the NIH (and NCI) conducts and supports basic, applied, and clinical and health services research to understand the processes underlying human health and to acquire new knowledge to help prevent, diagnose, and treat human disease and disabilities. This may include developing an information campaign such as the *Pap Tests: A healthy habit for life* campaign and evaluating its effectiveness at achieving its goal. NCI also has a mandate to disseminate research findings so that when the development and evaluation are completed, other Federal and state agencies, and private sector organizations, may take this information and apply it accordingly. NCI, therefore, plays an integral role in these activities.

The NCI disseminates research findings widely through scientific publication, press conferences, press statements, clinical alerts, patient education materials, meetings of professional societies, television and radio, the World Wide Web, our toll-free Cancer Information Service, our PDQ databases, and the Information Associates Program. Our staff has many contacts within agencies for a variety of programs and issues. Through these personal contacts, and those mechanisms mentioned above, Federal agencies and offices have direct access to information pertinent to their programs. In addition, we maintain and foster close working relationships with other Institutes that have formal collaborative relationships with the Office os Population Affairs-our projects and programs are thus included in that broad knowledge base. NCI has several partnerships with other federal agencies and non-federal groups to enhance our information dissemination activities. Following are examples of two specific information campaigns on cervical cancer:

Pap Tests: A healthy habit for life: In May 1998 the Office of Cancer Communications began a campaign to alert the public of the results of a survey that showed that older women were unaware of their continued risk for cervical cancer. National activities have included focusing on minority media outreach and the distribution of a media packet that focused on cervical cancer and older women. Additionally, NCI collaborated with the Healthcare Financing Administration (HCFA) to reprint an NCI cervical cancer publication with Medicare information for older women to be distributed through HCFA and NCI networks. Other activities have included conducting research with physicians to identify their attitudes and perceptions of Pap test screening among women 65 and older. Based on this research, a print public service announcement and newsletter article are being developed that encourage physicians to talk to their older patients about Pap test screening. These materials will be promoted through physician publications and newsletters.

The Pap Test and Cervical Cancer Video: An intertribal video on the early detection of cervical cancer for American Indian Women was produced by the NCI in conjunction with the Nebraska Department of Health. The video comes with educational material to help inform American Indian women of the importance of regular Pap tests.

Question 9. Please name the NCI liaisons with CDC, HRSA, and the Office of Population Affairs. Has NCI coordinated activity with the Title V Abstinence Education Grant Program or the Title XX programs within those agencies?

Response. As previously stated, NCI staff has many contacts within agencies for a variety of programs and issues. Liaisons with CDC, HRSA and the Office of Population Affairs vary on the program and issue involved.

NCI has not formally collaborated specifically on Title V Abstinence Education Grant program or the Title XX programs. As a research agency, NCI's role is to conduct and support research, then disseminate widely, new knowledge gained. This is done through information campaigns like the *Pap Tests: A healthy habit for life* campaign.

Question 10. What is the amount of research dollars spent by NCI on HPV as compared to the virus that causes AIDS? How many women die annually in the United States from cervical cancer? How many women die annually in the United States from AIDS?

Response. There are over 80 types of HPV, about 15 of which are associated with cancer of the cervix. NCI estimates that it will spend about $38 million on cervical cancer-related HPV research, and about $235 million on AIDS related cancers, in FY 1999. There are about 5,000 deaths in the U.S. from cervical cancer each year, and more than 200,000 deaths world wide. Over 90 percent of these cancers are HPV-related. There were about 4,600 female deaths in the U.S., and 900,000 worldwide, from HIV-related illness in FY 1997.

Question 11. On January 12, 1999, Chairman Bliley sent a letter to the NCI on women's health issues, including cervical cancer. In response to that letter, NCI estimated the number of Americans with HPV to be 24 million. In testimony before this committee by Dr. Ronald Valdiserri, of the Centers for Disease Control and Prevention (CDC), on March 16, 1999, he indicated that number is 45 million. Can you explain the discrepancy in numbers?

Response. The NCI estimated number of Americans with HPV came from the CDC website. The entry title is "The Challenge of STD Prevention in the U.S." and it was written in November 1996. CDC was not contacted by NCI for verification of this number and the CDC testified using an estimated number that may be more current than the one posted. Once again, it is important to remember that estimating the prevalence of HPV is difficult. Prevalence depends on many factors which include: the population screened, the sexual habits of those screened, what is classified as HPV infection at the time of screening, etc.

Question 12. In the above referenced letter from NCI to Chairman Bliley, NCI stated that, "*Condoms are ineffective against HPV because the virus is prevalent not only in mucosal tissue (genitalia) but also on dry skin of the surrounding abdomen and groin and it can migrate from those areas into the vagina and cervix.*" That letter went on to say that "*additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted.*" To the contrary, Dr. Ronald Valdiserri of CDC testified on March 16, 1999 that "Several studies have shown condoms to provide some protection against cervical cancer..." Can you explain the difference in conclusions made by CDC and NCI?

Response. The NCI conclusion that condoms are ineffective against HPV infection is based on the results of several long term studies which have failed to show that barrier contraceptives prevent cervical HPV infection, dysplasia, or cancer (Attachment 1, 2, 3). Dr. Valdiserri's testimony might be based on studies that show that while condoms are ineffective in preventing transmission of HPV, they are quite effective at preventing transmission of HIV and other sexually transmitted diseases. CDC would be able to provide insight into the basis of Dr. Valdiserri's statement.

Please do not hesitate to contact me if you have further questions.

Sincerely,

DR. DOUGLAS LOWY
Deputy Director, Division of Basic Sciences, NCI

Enclosures

ATTACHMENT 1

Original Articles

Barrier and Spermicidal Contraceptive Methods and Risk of Invasive Cervical Cancer

Allan Hildesheim,[1] Louise A. Brinton,[1] Katherine Mallin,[2] Herman F. Lehman,[3] Paul Stolley,[4] David A. Savitz,[5] and Robert Levine[6]

The effects of barrier and spermicidal methods of contraception on cervical cancer risk were examined by studying 479 cases of histologically confirmed invasive cervical cancer cases and 788 random digit dialing controls. In addition to a detailed history of contraceptive practices, information was available on numerous potential confounders, including demographic characteristics, sexual behavior, reproductive factors, Pap smear screening history, and smoking. After adjustment for relevant confounders, diaphragm and condom use were found not to be significantly associated with risk of cervical cancer. Although there was a small reduction in risk (OR = 0.8) associated with long-term use (5+ years) of the diaphragm, the effect appeared to relate to concomitant spermicide use, since there was evidence of further decreases in risk for women using spermicides alone for extended periods (OR = 0.7 for 5+ years). Effects were only seen among subjects of higher income and education levels, suggesting that patterns of usage may be important. The potential ability of spermicides to reduce cervical cancer risk by neutralizing viral agents warrants further attention. (Epidemiology 1990;1:266–272)

Keywords: Cervical cancer, contraception.

The strong and consistent association between sexual behavior and invasive cervical cancer (1) has led to the suggestion that a sexually transmitted agent is involved in the etiology of this disease. Two agents in particular have been extensively studied: herpes simplex virus type 2 and human papillomaviruses (2,3).

Given the possible infectious nature of cervical cancer, it is of interest to examine the possible protective effect of contraceptive methods. Specifically, barrier methods of contraception (mainly the diaphragm and/or condom) provide a physical barrier that could reduce the likelihood of infection by sexually transmitted agents and consequently reduce the risk of developing cervical cancer. Also likely is that use of spermicides (foam, jelly, and/or cream) reduce the risk of cervical cancer by protecting users from acquiring sexually transmitted diseases. Spermicides contain surfactants, mainly nonoxynol-9 (4), which have been shown to neutralize HSV-2 (5,6), as well as other venereal agents (7,8). In addition to the role of each contraceptive method in isolation, use of spermicidal agents in conjunction with barrier methods might further protect against cancer of the cervix.

Previous studies of barrier contraceptives and spermicides in relation to invasive and preinvasive cervical cancer have yielded conflicting results. Many studies (9–16), but not all (17–19), have reported an inverse relation between diaphragm and/or condom use and cervical cancer risk. In addition, four studies (9,12,14,17) have detected a negative relation between vaginal spermicide use and cervical cancer, although one study that also examined this issue did not detect an association (19).

Of the studies mentioned above, only two were capable of controlling for potential confounding by both sexual and screening behavior (12,17). Both of these were studies of invasive cervical cancer. Celentano et al (17) reported a 70% reduced risk of invasive cervical cancer among women who reported ever use of a vaginal spermicide compared with never users of spermicides. Unfortunately, this study was unable to assess the effect of duration of spermicide use on risk of cervical cancer. Peters et al (12) reported a 7% reduction in risk of invasive cervical cancer per year of use of a barrier method of contraception (defined as condom, diaphragm, and/or spermicide). Although results are not

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presented in detail, Peters et al also noted that women who used vaginal spermicides without a diaphragm appeared to be at a lower risk of invasive cervical cancer than those who used the diaphragm without vaginal spermicides.

In an attempt to assess the effect of barrier and spermicide methods of contraception on risk of cervical cancer, we obtained information regarding lifetime birth control practices from invasive cervical cancer cases and community controls in five regions of the United States. The availability of information on numerous potential confounders, including demographic characteristics, sexual and reproductive factors, Pap smear screening history, smoking, and use of other contraceptive methods, allowed us to examine the effects of barrier and spermicide use independent of other known cervical cancer risk factors.

Methods

Between April 1982 and January 1984, women 20–74 years of age with newly diagnosed invasive cervical cancer were recruited from 24 participating hospitals in 5 areas reporting to the Comprehensive Cancer Patient Data System (Birmingham, Chicago, Denver, Miami, and Philadelphia).

Community controls were obtained through random digit dialing techniques (20). Controls were individually matched to cases on age (within 5 years), race, and telephone exchange. Two controls were selected per case. More details of the selection process are provided elsewhere (21).

A total of 658 eligible cases and 1114 controls were ascertained. Home interviews were conducted by trained interviewers who obtained information on contraceptive practices, sociodemographic characteristics, pregnancy history, menstrual history, hygiene practices, sexual behavior, medical events, smoking, diet, marital history, and family history of cancer. Information on birth control use was obtained by using lifetime calendars to record usage of specific methods on a monthly basis in the context of other relevant life events such as age at menarche, age at first intercourse, pregnancies, and age at menopause.

Interviews were successfully obtained from 481 cases (73.1%) and 801 controls (71.9%). Nonresponse was accounted for by refusal (9.7% of cases, 21.9% of controls), subjects having moved or being unlocatable (3.8%, 3.4%), death (5.0%, 0.5%), illness (2.1%, 1.1%), and other problems (1.7%, 1.1%). In addition, physician consent was not obtained for 4.6% of cases. The final groups used in the analysis consisted of 479 cases and 788 controls for whom complete contraceptive history was available.

The odds ratio (OR), as an estimator of the relative risk, was the measure of association used to determine the relation between contraceptive usage and cervical cancer. Unconditional logistic regression analysis provided adjusted ORs and 95% confidence intervals (CI) (22). Conditional logistic regression (23) that retained the matching of cases and controls yielded similar estimates. We present results from unconditional logistic regression in this report, since use of conditional regression analyses involved the exclusion of 22% of study subjects owing to missing matches.

Results

Table 1 describes the contraceptive practices among the 610 (77%) community controls enrolled in the study who reported use of contraceptive methods and illustrates the frequent use of combinations of birth control methods. Seven methods of contraception were examined: vaginal spermicides, the diaphragm, condoms, oral contraceptives, intrauterine devices (IUDs), female sterilization, and vasectomy. The majority of these controls (75%) reported use of two or more methods. A total of 22% of users reported the use of four or more different methods in their lifetime.

Among 293 women reporting ever use of vaginal spermicides, only 10 (3%) used it as the sole method of birth control, while 227 (77%) also reported use of barrier methods of contraception. Less than 1% of 164 women reporting diaphragm use and 15% of 287 women reporting condom use used these methods exclusively.

Tables 2 and 3 present the risk of cervical cancer associated with use of specific birth control methods. Initially, barrier methods of contraception appeared to be associated with reduced risks of cervical cancer. However, after controlling for age, race, education, income, interval since last Pap smear, and lifetime number of sexual partners, the effect nearly disappeared. Thus, the risk associated with ever use after adjustment was 1.2 (95% CI = 0.9,1.6). In addition, after adjustment, no significant trend was observed with increased duration of use of barrier methods (p for trend = 0.68), short-term users (<5 years) having an OR of 1.4 and long-term users an OR of 0.9. Further adjustment for duration of oral contraceptive use or smoking did not alter these or any other observed estimates.

When barrier methods of contraception were separated into diaphragm and condom use (Table 2), there was no effect on risk for condom use, but some evidence of decreased risk associated with diaphragm use. Risk

TABLE 1. Contraceptive Practices among 610 Community Controls Reporting Birth Control Use

			Pairwise Birth Control Use with						
	Total	Only	Vaginal Spermicide	Diaphragm	Condom	Oral Contraceptive	IUD	Female Sterilization	Vasectomy
Vaginal spermicides	293	10	—	154	157	199	82	64	37
Diaphragm	164	1	154	—	87	99	44	28	25
Condom	287	44	157	87	—	183	64	51	41
Oral contraceptives	403	56	199	99	183	—	113	90	64
IUD	151	10	82	44	64	113	—	43	18
Female sterilization	151	29	64	28	51	90	43	—	1
Vasectomy	85	5	37	25	41	64	18	1	—

	Number of Birth Control Methods Used in Lifetime						
	1	2	3	4	5	6	TOTAL
Number of women	155	174	148	86	39	8	610
Percentage	25.4	28.5	24.3	14.1	6.4	1.3	100

TABLE 2. Risk of Invasive Cervical Cancer Associated with Barrier Contraceptive Use

	Cases*	Controls*	OR†	OR‡	CI
Barrier methods§					
Never	281	418	1.0	1.0	
Ever	182	356	0.8	1.2	[0.9,1.6]
Never	281	418	1.0	1.0	
<5 years	124	223	0.9	1.4	[1.0,1.8]
5+ years	58	133	0.6	0.9	[0.6,1.4]
Trend			$p = 0.004$	$p = 0.68$	
Diaphragm§					
Never	401	613	1.0	1.0	
<5 years	46	123	0.6	0.9	[0.6,1.3]
5+ years	16	38	0.6	0.8	[0.4,1.6]
Trend			$p = 0.002$	$p = 0.36$	
Condom§					
Never	317	494	1.0	1.0	
<5 years	104	189	1.0	1.2	[0.9,1.7]
5+ years	42	91	0.6	1.0	[0.6,1.5]
Trend			$p = 0.05$	$p = 0.62$	

* Women with missing values are excluded from analysis.

† Adjusted for age.

‡ Adjusted for age, race, education, income, interval since last Pap smear, and lifetime number of sexual partners.

§ Many users of barrier methods also used spermicides, either synchronously or asynchronously.

decreased slightly with increasing duration of use, but the trend was not statistically significant (p for trend = 0.36).

Table 3 presents the risk of cervical cancer associated with use of vaginal spermicides. After adjusting for confounding factors, spermicide users were at a similar risk of disease as nonusers (OR = 1.0; 95% CI = 0.7,1.3). When duration of use was examined, no significant trend of risk with increasing duration of use was observed (p for trend = 0.71), long-term users having an OR of 0.9 (95% CI = 0.5,1.4). However, when spermicide use was restricted to those women who reported

TABLE 3. Risk of Invasive Cervical Cancer Associated with Vaginal Spermicide Use

	Cases*	Controls*	OR†	OR‡	CI
Vaginal spermicides§					
Never	331	486	1.0	1.0	
Ever	132	288	0.7	1.0	[0.7,1.3]
Never	331	486	1.0	1.0	
<5 years	102	216	0.8	1.0	[0.7,1.4]
5+ years	30	72	0.6	0.9	[0.5,1.4]
Trend			$p = 0.009$	$p = 0.71$	
Spermicide without barrier					
Never	383	605	1.0	1.0	
<5 years	69	140	0.9	1.0	[0.7,1.4]
5+ years	11	29	0.7	0.7	[0.3,1.5]
Trend			$p = 0.19$	$p = 0.51$	

* Women with missing values are excluded from analysis.

† Adjusted for age.

‡ Adjusted for age, race, education, income, interval since last Pap smear, and lifetime number of sexual partners.

§ Includes women who used vaginal spermicides alone, as well as women who used vaginal spermicides with the diaphragm or condom.

using vaginal spermicides without the simultaneous use of a barrier method (vaginal spermicide only use), long-term users had a slightly reduced cervical cancer risk (OR = 0.7; 95% CI = 0.3,1.5), although the test for trend was not significant ($p = 0.51$).

Given the possibility that timing, in addition to duration, of birth control use might be of importance, the period of contraceptive usage was examined in relation to the date of diagnosis of the case (and comparable data for controls). Five-year periods of time were constructed starting from the date of diagnosis of the case and moving backwards in time. Within each 5-year period, women reporting 6 or more months of use of a given method were compared with those reporting no use of the same method during the same period. No time periods could be identified where the varying methods of birth control had distinct effects.

Women who report never having used any birth control may be an inappropriate reference for comparison with women who report using methods of contraception, owing to wide differences in patterns of health care, sexual behavior, and socioeconomic status (SES). This concern led us to investigate the issue more closely. A total of 31% of the cases reported never using any method of birth control compared with 23% of the controls, yielding an OR of 1.5. When controls who reported no contraceptive usage were investigated, they were found to be more likely than controls who reported having used contraceptives to be poor, uneducated, black, and never to have been screened for cervical cancer. We detected significant differences with regard to number of lifetime sexual partners. Despite these differences, excluding women who never used contraceptives from the analyses did not markedly alter the adjusted estimates of risk, and conclusions drawn from the data remained unchanged.

The effect of excluding women who had ever used oral contraceptives was examined in analyses comparing users of nonhormonal contraceptives with each other. Although no significant trends were observed, long-term vaginal spermicide only users were found to be at a 70% decreased risk of disease (OR = 0.3; 95% CI = 0.06,1.1).

Because of concerns regarding the accuracy and consistency of use of contraceptive methods, we examined contraceptive users and nonusers within different categories of income and education (Table 4). Women with 0–11 years of education and ≤$20,000 yearly income were classified as low SES. Those with 12+ years of education and income >$20,000 were classified as high SES, and the remainder were classified as medium SES. When analysis was performed stratified by SES, barrier and spermicidal contraceptive use among low and medium SES women did not appear to be associated with reduced risks. Among low SES women, long-term vaginal spermicide users were at a 1.7-fold excess risk, but this effect was not statistically significant. Among high SES women, a significant dose response of decreasing risk with increasing duration of use was observed among spermicide users (OR = 0.5 for long-term users; p for trend = 0.03). Furthermore, the reduction in risk was strongest among women who reported use of vaginal spermicides without simultaneous use of barrier methods (OR = 0.3 for long-term users; P for trend = 0.05).

TABLE 4. Risk of Invasive Cervical Cancer Associated with Birth Control Use, by Socioeconomic Status

	Low SES*		Medium SES		High SES	
	OR†	Cases‡	OR	Cases	OR	Cases
Vaginal spermicides						
Never used	1.0	(148)	1.0	(92)	1.0	(73)
<5 years	1.1	(31)	1.1	(39)	0.7	(30)
5+ years	1.7	(10)	1.0	(8)	0.5	(11)
p for trend	$p = 0.40$		$p = 0.72$		$p = 0.03$	
Vaginal spermicide alone						
Never used	1.0	(157)	1.0	(110)	1.0	(97)
<5 years	1.3	(28)	1.1	(25)	0.7	(14)
5+ years	1.1	(4)	0.9	(4)	0.3	(3)
p for trend	$p = 0.52$		$p = 0.88$		$p = 0.05$	
Diaphragm						
Never used	1.0	(174)	1.0	(121)	1.0	(86)
<5 years	2.4	(11)	0.6	(14)	0.7	(21)
5+ years	1.1	(4)	1.1	(4)	0.6	(7)
p for trend	$p = 0.27$		$p = 0.40$		$p = 0.12$	
Condom						
Never used	1.0	(150)	1.0	(88)	1.0	(64)
<5 years	1.3	(29)	1.2	(35)	1.2	(36)
5+ years	0.7	(10)	1.1	(16)	1.0	(14)
p for trend	$p = 0.89$		$p = 0.62$		$p = 0.68$	

* Low SES = 0–11 years education and ≤20K yearly income. Medium SES = (0–11 years education and >20K income) or (12+ years education and ≤20K income). High SES = 12+ years education and >20K income.
† Adjusted for age, race, interval since last Pap smear, and lifetime number of sexual partners.
‡ Women with missing values are excluded from analysis.

Among high SES women, there was also evidence of decreased risk associated with long-term diaphragm use. The trend, however, was not statistically significant ($p = 0.12$). Among condom users, no protective effect was detected.

Analysis was also conducted stratifying by number of lifetime sexual partners, under the assumption that women who report multiple partners would have greater benefits from use of barrier and spermicidal contraceptive methods. No differences were observed when ORs obtained from the main analysis and those obtained from the stratified analysis were compared (data not shown).

Discussion

Previous studies have reported reduced risks of cervical cancer associated with barrier (9–16) as well as spermicide (9,12,14,17) methods of contraception. Few studies, however, have been able to adjust appropriately for confounding variables (12,17). Adjustment for Pap smear screening history, SES, and sexual behavior is essential when assessing the effect of birth control methods on risk of cervical cancer, as has been shown in our previous report of the effect of oral contraceptive use on risk of invasive cervical cancer (21).

Indeed, education and interval since last Pap smear were strong confounders of the association of birth control use and cervical cancer, while lesser confounders were income and number of sexual partners. Adjustment for these factors brought the estimates of risk associated with barrier and spermicidal methods of contraception close to unity. Additional adjustment for duration of oral contraceptive use and smoking had little effect on the risk estimates. Thus, although both condom and diaphragm use appeared initially to be associated with a reduced risk of cervical cancer, these effects were essentially eliminated by adjustment for confounding factors.

Initial examination of spermicide use showed an apparent protective effect on the risk of invasive cervical cancer, although adjustment for confounding factors eliminated this association. Further assessment of usage within categories of SES, however, revealed that women of high SES who used vaginal spermicides were at a significantly reduced risk of invasive cervical cancer. Although a similar, but nonsignificant effect was observed for diaphragm users, the observation that high

SES women who used vaginal spermicides without concomitant use of a barrier methods were at a lower risk than those who used spermicides with a barrier method suggests that the spermicide and not the diaphragm protects against disease. Furthermore, 92% of diaphragm users reported also using vaginal spermicides, indicating that the nonsignificant decrease in risk observed among women of high SES who reported diaphragm use could result from the effect of the spermicide on risk. In addition, our finding that long-term vaginal spermicide only users were at a 70% decrease in risk when compared with other nonhormonal contraceptive users further strengthens the hypothesis that the reduction in risk is from spermicide rather than diaphragm use.

A possible explanation for this subgroup effect is that women of higher SES and those who use spermicides alone are more likely to use the spermicide consistently or more likely to use larger quantities of spermicide. Also, data obtained from higher SES women might be more accurate and ORs obtained from this subset of women might be better estimators of the association of birth control use and cervical cancer. Caution, however, must be exercised in interpreting these results, given the small numbers of women involved and also the possibility of confounding by sexual behavior of the male partners of women, a variable not assessed in this study.

The lack of a significant protection provided by the diaphragm might also be explained by the fact that the diaphragm traps some of the spermicide close to the cervix, reducing the effectiveness of the spermicide to protect against viral infection of the vaginal vault. Various agents, including those believed to be linked causally to cervical cancer (HSV-2 and HPV), are capable of infecting the vagina and vulva (24–28). The vaginal vault may thus become infected during intercourse, and the infection may spread to the cervix after removal of the diaphragm.

Condom use has traditionally been regarded as a physical barrier that protects the vaginal vault from infection during sexual intercourse. Our observation that condom use does not reduce the risk of cervical cancer might be interpreted as indicating that the condom is not always used appropriately. Sexual contact prior to the placement of the condom would eliminate its protective effect. In this study we were unable to assess directly the reliability of use of condoms. Stratification by SES variables did not suggest any differential use patterns among high and low SES women. Another possible explanation for the lack of protection provided by the condom is that areas of the base of the penile shaft may not be shielded by the condom, and any infections in this area may be transmitted to the female partner. A previous report (29) has demonstrated that high proportions of male HPV infections occur in the penile shaft.

In summary, after adjustment for confounding in this study, neither diaphragm nor condom use appeared to reduce substantially the risk of invasive cervical cancer. A protective effect of vaginal spermicide use among high SES women was suggested by the data; the effect was strongest among women who used spermicides without the diaphragm. Although a reduction in cervical cancer risk among women reporting spermicide use is biologically plausible based on its proven antiviral effects, further investigations are needed to confirm the relationship.

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ATTACHMENT 2

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RISK FACTORS FOR CERVICAL CANCER IN GREENLAND AND DENMARK: A POPULATION-BASED CROSS-SECTIONAL STUDY

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The incidence of cervical cancer in Greenlandic women aged 20–39 years is nearly 6 times higher than in Danish women of the same age. Possible determinants of cervical cancer incidence were investigated in a population-based cross-sectional study. From Nuuk (Greenland) and Nykøbing Falster (Denmark) a sample of 800 women aged 20–39 years was drawn at random. A total of 586 and 661 women were studied in Greenland and Denmark, respectively. All underwent a personal interview. In Greenland, 13% of the women reported first intercourse before the age of 14 in contrast to 3.5% in Denmark, and nearly 85% of the Greenlanders had their sexual debut before the end of the 16th year of age whereas this applied to only 45% of the Danish women. The prevalence of women with 0–1 lifetime sexual partner was 20.4% in Denmark, and only 1.7% in Greenland. In contrast, 53.2% of the Greenlandic women reported more than 20 partners and 22.4% more than 40 partners. The corresponding figures for Denmark were 3.6% and 0.3%, respectively. In Greenland the most common contraceptive method was the use of intra-uterine devices (73.6%), whereas, in Denmark, oral contraceptive use was most frequent (87.9%). Few Greenlanders had ever used "barrier" contraceptives (diaphragm: 1.4%; condom: 18.1%) compared to Denmark (diaphragm: 10.1%; condom: 53.9%). As many as 87.4% were current smokers in Greenland (Denmark: 53.6%) and 5.6% claimed to have never smoked, whereas this applied to 35.3% in Denmark. The indications of a higher sexual activity (multiple partners, early age at first intercourse) in Greenland compared to Denmark are in line with the observed higher rates of sexually transmitted diseases and with the hypothesis that differences in cervical cancer incidence between Greenland and Denmark are determined by aspects of sexual background.

Several studies of the sexual behaviour of women in relation to cervical cancer (Martin, 1967; Rotkin, 1973; Harris *et al.*, 1980; Reeves *et al.*, 1985) point to an infectious element in the pathogenesis of this cancer. Results from molecular biological research supplemented with observations in humans have indicated that specific types of human papillomavirus (HPV) may be of aetiological importance (Muñoz *et al.*, 1988). It has been suggested that HPV may be a prerequisite but not a sufficient cause of cervical cancer (zur Hausen, 1986). This was underlined by our recent finding that there was no straightforward correlation between the prevalence of HPV infection and cervical cancer incidence in Greenland and Denmark (Kjaer *et al.*, 1988). Attention should therefore be paid to the importance of other infections as well as to the possible joint action of infectious and non-infectious factors.

Little is known about the variation in frequency of these factors or of differences in sexual behaviour between populations with contrasting cervical cancer incidence. In addition to examining the prevalence of specific types of HPV in Greenland and Denmark, we determined the prevalence of certain habits concerning sexual life, smoking, and use of contraceptives in women aged 20–39 in these areas. In the present re- to 6-fold difference in the incidence of cervical cancer (Kjaer *et al.*, 1988).

MATERIAL AND METHODS

Study population and enrollment

From February to September 1986 a population-based cross-sectional study was conducted on random samples of women in a high-risk area for cervical cancer (Nuuk, Greenland) and a low-risk area (Nykøbing Falster, Denmark). In 1975–84 the cumulative incidence rate was 5.7 times higher in Greenlandic women 20–39 years of age than in Danish women belonging to the same age-group (Kjaer *et al.*, 1988). A detailed description of the age-distribution of the population sample, eligible women and study participants has been provided (Kjaer *et al.*, 1988).

Greenland. Greenland is a part of the Danish kingdom. The indigenous population is of Inuit origin with a European (Caucasian) intermixture of approximately 25–30% (Kissmeyer-Nielsen, 1971). A total of 800 women aged 20–39 years, born in Greenland and resident in Nuuk municipality, was drawn at random from the computerized Danish Central Population Register. Of these women, 104 had moved out of the municipality and one had died, leaving 695 eligible for study. A total of 586 women (84.3%) were included in the study; 93 (13.4%) could not be reached, and 16 (2.3%) refused to participate.

Denmark. The Danish population is entirely Caucasian. From the Central Population Register a random sample of 800 women 20–39 years of age was drawn from the population of the municipality of Nykøbing Falster. Prior to our approach, 14 women had moved out of the area, and one had died, leaving 785 women eligible for investigation. A total of 661 women (84.2%) were enrolled; 58 (7.4%) could not be contacted, and 66 (8.4%) refused to take part in the study.

Interviews

General information about the study was provided through local news media (newspapers, radio). Then, each woman was invited by letter for a personal interview (and gynaecological examination) at the local health clinic or hospital. Reminders were sent after 2–3 weeks and non-responders were finally contacted by phone (Nykøbing Falster) or by a personal messenger (Nuuk). In each area, an *ad hoc* field team consisting of a female doctor (B.J. Haugaard in Greenland and C. Teisen in Denmark) and a nurse (all of the same age as the invited women) conducted all the interviews using a structured questionnaire which covered information about marital status, current and past smoking habits, contraceptive use, previous

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smear history, gynaecological operations, age at first intercourse, and number of sexual partners. Every effort was made to ensure that the interviews were conducted in the same way in the 2 areas.

Statistical analysis

Crude prevalence rates for Greenland and Denmark were compared using a normal approximation to the exact Fisher test for equality of the probability parameters in 2 binomially distributed random variables.

Prevalence odds ratios for the different factors were calculated for Greenlandic women compared to Danish women using the logistic regression methods of Rothman (1986). The prevalence odds are defined as the odds of having a certain characteristic relative to those of not having it. The odds ratios were standardized for age by including age in the regression equation besides the factor in question. The statistical package Genstat was used for the calculations (Alvey *et al.*, 1983).

RESULTS

Background characteristics

Marital status

There are significant differences between the 2 populations concerning marital status (Table I), both overall and in the different age-strata. Some 75.6% of Danish women were living in a matrimonial relationship (marriage: 43.7%; cohabitation: 31.9%). In Greenland altogether 82.7% were either married (21.3%) or cohabited (61.4%). A statistically significantly ($p < 0.005$) lower prevalence of women who had never married or cohabited was observed in Greenland (10.4%) than in Denmark (16.8%). The total prevalence of divorced and widowed women was of the same magnitude in the 2 areas (Greenland: 6.8%; Denmark: 7.6%).

Sexual characteristics

Age at first intercourse

The age at starting sexual life is very different between Danish and Greenlandic women (Table II). Thirteen percent of the women in Greenland had their first intercourse before the age of 14, in contrast to only 3.5% of the Danish women. While less than 1% of the women in Greenland were over 20 at first intercourse, the proportion of Danish women in this group was nearly 10 times higher (9.2%). Nearly 85% of the Greenlandic women had their first intercourse before the end of the 16th year of age, whereas a significantly lower proportion (45.4%) ($p < 0.001$) of the Danish women belonged to this category.

Figure 1 reflects the tendency towards younger age at first intercourse among younger cohorts. The age-specific rates for women with early sexual debut (≤13 years) thus showed a decreasing prevalence with increasing age in both populations, particularly in Greenland where rates were higher in all age-groups, and so did the proportion of women aged 14–16 years in Denmark. As a consequence, the proportion of women starting sexual life at 17–19 years increased with increasing age in both areas.

Number of partners

In the Danish study group as a whole, 20.4% reported 0–1 lifetime sexual partner, whereas this applied only to 1.7% of the women in Greenland (Table II). In Denmark 3.6% reported more than 20 partners. In contrast, more than half of the Greenlandic women (53.2%) belonged to this group. The observed, highly significant difference ($p < 0.005$) in number of sexual contacts was not changed by age-standardization. Only 2 women (0.3%) in Denmark claimed to have had more than 40 sexual partners, compared to 131 (22.4%) of the Greenlandic women. Of these, 39 (20.2%) were 20–24 years old, 42 (24.6%) 25–29 years, 31 (24.4%) 30–34 years, and 19 (20.0%) were 35–39 years of age (Fig. 2).

In both Greenland and Denmark the prevalence of 0–1 partner was highest in the youngest age group (20–24 years), and in the oldest (35–39 years). In all age-groups Denmark had the significantly highest rate (Fig. 2).

The Greenlandic prevalence rate of more than 20 sexual partners was as high as 55–60% among women aged 20–34 years and 43.2% in the age-group 35–39 years (Fig. 2). In Denmark, the proportion of women with more than 20 partners was of the same magnitude in all age-groups (less than 6%) and lower than in Greenland in a statistically highly significant way ($p < 0.001$).

In both Greenland and Denmark, women whose sexual debut occurred before the age of 17 reported significantly more sexual partners than women with a later debut (Table III). A significantly higher proportion of the Greenlandic women had an early sexual debut (≤16 years), independently of the total number of sexual partners, compared to Danish women.

Contraception

The method of contraception most often used in Denmark

TABLE I – AGE-SPECIFIC PREVALENCE RATES OF MARITAL STATUS IN NYKØBING FALSTER (DENMARK) AND NUUK (GREENLAND)

Age (years)		Married		Cohabited		Unmarried, never cohabited		Divorced or widowed	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
20–24	D[1]	11	(6.7)	94	(56.6)	60	(36.1)	1	(0.6)
	G[2]	11	(5.7)	138	(71.5)	44	(22.8)	0	—
25–29	D	40	(30.3)	61	(46.3)	25	(18.9)	6	(4.5)
	G	36	(21.1)	123	(71.3)	8	(4.6)	4	(2.4)
30–34	D	99	(57.6)	36	(20.9)	16	(9.3)	20	(11.0)
	G	39	(30.7)	64	(50.4)	5	(3.9)	19	(13.0)
35–39	D	139	(72.8)	20	(10.5)	9	(4.7)	23	(11.5)
	G	39	(41.1)	35	(36.8)	4	(4.2)	17	(17.9)
Total	D	289	(43.7)***	211	(31.9)***	110	(16.8)**	50	(7.6)*
	G	125	(21.3)	360	(61.4)	61	(10.4)	40	(6.8)

[1]D = Denmark.–[2]G = Greenland.–*p-value for difference between Denmark and Greenland > 0.05; **p-value for difference between Denmark and Greenland < 0.005; ***p-value for difference between Denmark and Greenland < 0.001.

TABLE II – PREVALENCE RATES AND AGE-STANDARDIZED PREVALENCE ODDS RATIOS OF POTENTIAL RISK FACTORS FOR CERVICAL CANCER IN GREENLANDIC AND DANISH WOMEN 20–39 YEARS OF AGE

Characteristics	Greenland		Denmark		Age-standardized odds ratio (Greenland/Denmark)	(95% CI)
	n	(%)	n	(%)		
Age at first intercourse						
≤13	76	(13.0)	23	(3.5)	3.20	(1.90–5.20)
≥20	5	(0.9)	61	(9.2)	0.09	(0.04–0.24)
Number of partners						
0–1	10	(1.7)	135	(20.4)	0.14	(0.07–0.28)
≥20	312	(53.2)	24	(3.6)	23.90	(15.40–37.10)
Contraception (ever)						
None	80	(13.7)	22	(3.3)	4.30	(2.60–7.00)
OC[1]	300	(51.2)	581	(87.9)	0.15	(0.11–0.19)
IUD[2]	431	(73.6)	270	(40.9)	4.90	(3.90–6.50)
→ Condom	106	(18.1)	356	(53.9)	0.19	(0.15–0.25)
Diaphragm	8	(1.4)	67	(10.1)	0.15	(0.07–0.32)

[1]OC = oral contraceptives.–[2]IUD = intrauterine device.

was oral contraception (OC) (Table II). The age-specific curves for Denmark and Greenland (Fig. 3) were similar, but the Danish rates were significantly higher than the Greenlandic ones. In Greenland, most of the women who had ever used this kind of contraception had used it for less than 2 years (68.7%), while in Denmark the majority of women (ever users of OC), had used it for more than 5 years (48.0%).

In Greenland 73% of the women had at some time used intra-uterine devices (IUD) for contraception, while in Denmark the corresponding rate was 40.9% (Table II). The Greenlandic and Danish age-curves regarding IUD-users (Fig. 3) were parallel, only the age-specific rate in Greenland was significantly higher in every age group.

A fairly high proportion of the Greenlandic participants (13.7%) reported not using any kind of contraception, while this applied to only 3.3% of the Danish study population ($p < 0.001$) (Table II). This difference was significant in all age groups except for women 30–34 years of age (Fig. 3).

The prevalence of women who had ever used "barrier" methods (condom, diaphragm) was very low among the Greenlandic population (condom: 18.1%; diaphragm: 1.4%) (Table II). Statistically significantly greater numbers of Danish women

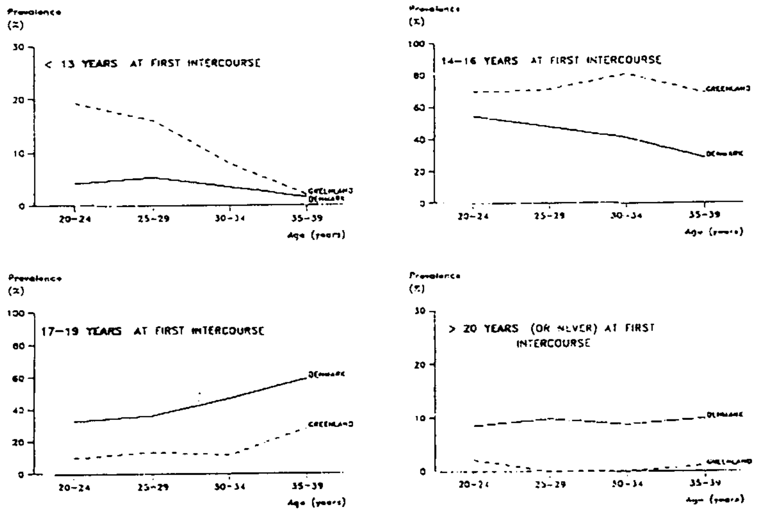

FIGURE 1 – Age-specific prevalence rates of age at first intercourse in Greenlandic and Danish women 20–39 years of age.

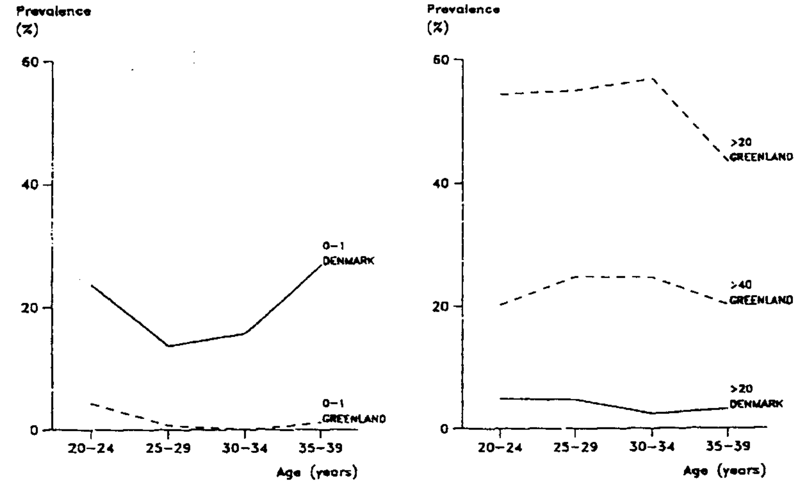

FIGURE 2 – Age-specific prevalence rates of total number of sexual partners in Greenlandic and Danish women 20–39 years of age.

had used these methods for contraception at some time (condom: 53.9%; diaphragm: 10.1%).

The age-curves for ever-use of the condom in Greenland and Denmark showed similar profiles (Fig. 4), the Danish curve only being at a significantly higher level. Concerning the use of the diaphragm, Danish women also had higher rates in all age-groups, but the difference between Greenland and Denmark was only statistically significant for women aged 35–39 years ($p < 0.001$).

Time period with unprotected cervix

The proportion (%) of sexually active life with "unprotected" cervix (*i.e.*, without use of condom or diaphragm) has been calculated as:

$$\frac{[\text{Age (years)} - \text{age at first intercourse (years)}] - (\text{years with use of condom or diaphragm})}{[\text{Age (years)} - \text{age at first intercourse (years)}]} \times 100.$$

In Greenland more than 80% had never used barrier-contraception such as condom or diaphragm in any period of their sexually active life. Statistically significantly fewer Danish women (39.5%) had never used barrier methods (*i.e.*, were 100% "unprotected") ($p < 0.001$). In Denmark 26.2% had been unprotected for 80–99% of their sexually active life, 18.2% for 50–79% and finally 13.3% of the Danish women had been unprotected for up to 49% of their sexual life. The corresponding figures for Greenland were 6.5% with no protection for 80–99% of the sexually active life, 3.6% unprotected for 50–79% and 4.7% for 0–49% of the time.

The overall profiles of the age-specific rates of the *exact* number of years with unprotected cervix were very similar in Greenland and Denmark (Fig. 5). In all 5-year age-groups the prevalence of women with few years of unprotected cervix was highest in Denmark, whereas absence of protection of the cervix for many years prevailed among the Greenlanders.

Smoking

Substantial differences are observed in smoking habits between the 2 populations (Table IV). A very high percentage of the Greenlandic women (87.4%) were current smokers in contrast to 53.6% of the Danish population ($p < 0.001$). A total of 41 women in Greenland (7.0%) had stopped smoking while

TABLE III – RELATIONSHIP BETWEEN AGE AT FIRST INTERCOURSE AND NUMBER OF SEXUAL PARTNERS IN GREENLANDIC AND DANISH WOMEN 20–39 YEARS OF AGE

Number of partners	Age at first intercourse (years)							
	Greenland[1]				Denmark[2]			
	≤16		≥17		≤16		≥17	
	n	(%)	n	(%)	n	(%)	n	(%)
0–1	5	(50.0)[3] (1.0)[4]	5	(50.0)[3] (5.6)[4]	33	(24.6)[3] (11.1)[4]	101	(75.4)[3] (28.2)[4]
2–9	72	(77.4)[3] (14.7)[4]	21	(22.6)[3] (23.6)[4]	194	(47.2)[3] (65.1)[4]	217	(52.8)[3] (60.6)[4]
≥10	412	(86.7)[3] (84.3)[4]	63	(13.3)[3] (70.8)[4]	71	(63.9)[3] (23.8)[4]	40	(36.1)[3] (11.2)[4]
Total	489	(100.0)	89	(100.0)	298	(100.0)	358	(100.0)

[1] 8 undefined.–[2] 5 undefined.–[3] Percent row (horizontal).–[4] Percent column (vertical).

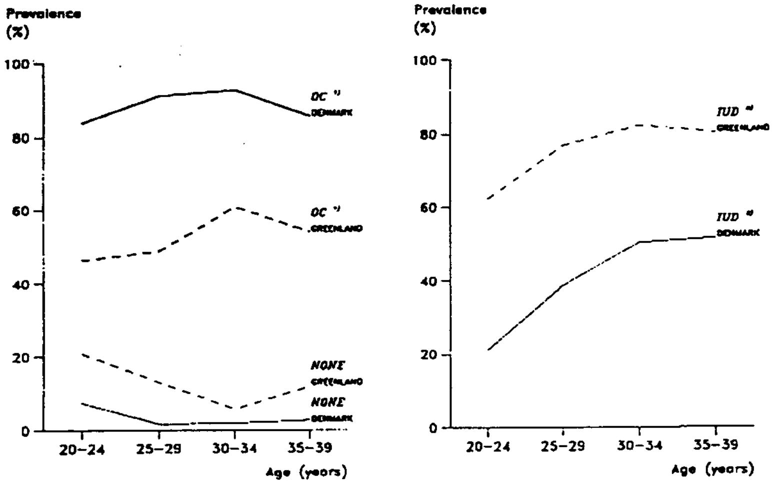

FIGURE 3 – Age-specific prevalence rates of non-barrier contraceptive methods (ever use) in Greenlandic and Danish women 20–39 years of age. OC, oral contraception; IUD, intrauterine devices.

statistically significantly more Danish women (11%) were ex-smokers ($p < 0.02$). These differences were found in all age-groups. Only 33 of the 586 women (5.6%) participating from Greenland had never smoked, compared with 35.3% of the Danish women ($p < 0.001$) (Table IV). No differences were observed with regard to age at starting smoking.

Lifetime cigarette consumption was calculated by multiplying the number of cigarettes smoked per day by the duration of smoking. One pack-year was then defined as 1 pack of cigarettes per day for a year. At the population level (Table IV) a significantly higher ($p < 0.001$) lifetime consumption of cigarettes was seen in Greenland than in Denmark. Among the Danish women, 311 (47.1%) were in the category of less than 2 pack-years, while this only applied to 188 (32.1%) of the Greenlanders. In contrast, 283 Greenlandic women (48.3%) belonged to the category of 2–9 pack-years, compared to 207 (31.3%) Danish participants. Nearly the same prevalence of heavy smokers (≥10 pack-years) was observed in the 2 areas.

Focusing on smokers (current) only, the pattern was somewhat different. In this case the Danish women appeared to have the highest consumption with 33.5% having used more than 10 pack-years in contrast to only 20.6% in Greenland. Nearly identical proportions had used 2–9 pack-years (48.5% in Denmark and 51.5% in Greenland), whereas a significantly lower ($p < 0.001$) prevalence of women smoking less than 2 pack-years appeared in Denmark (18.0%) compared to Greenland (28.0%).

While the proportions of heavy smokers (≥15 cigarettes per day) were very similar at all ages in Greenland and Denmark, the low proportions of non-smokers in Greenland were replaced by light (≤4 cigarettes per day) and moderate smokers (5–14 cigarettes per day) being significantly ($p < 0.001$) higher than in Denmark in all age-groups.

DISCUSSION

The sexual behaviour of women with cervical cancer tends in general to be characterized by early age at first intercourse, multiple sexual partners, sexual relations with men who themselves have multiple partners, and use of non-barrier contraceptives. Such features clearly point to the importance of sexually transmitted agents for the development of cervical cancer (Brinton and Fraumeni, 1986). In addition, smoking as well as a diet low in vitamin C and beta-carotene appears to increase the risk of cervical neoplasia (Wassertheil-Smoller *et al.*, 1981; Marshall *et al.*, 1983; La Vecchia *et al.*, 1984). Such risk factors for cervical cancer have primarily been demonstrated in analytical studies of a case-control nature, following indications of their importance from observations of the occurrence of cervical cancer in special populations; examples are the high incidence in prostitutes (Keighley, 1968), and the low incidence and mortality in nuns (Fraumeni *et al.*, 1969), in Jews (Boyd and Doll, 1964; Pridan and Lilienfeld, 1971), and in Mormons (Gardner and Lyon, 1977). A higher prevalence of these characteristics alone or in combination would be expected in populations with a high incidence of cervical cancer, compared with low-incidence populations.

Greenland has one of the highest incidence rates of cervical cancer on record in the world (Nielsen and Hansen, 1985) and in the age-group 20–39, the rates are 5 to 6 times higher in Greenland than in Denmark (Kjaer *et al.*, 1988). This marked

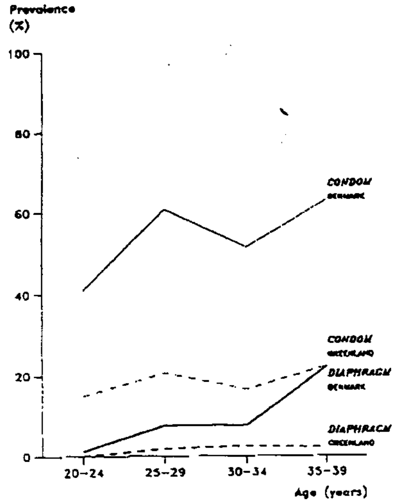

FIGURE 4 – Age-specific prevalence rates of barrier contraceptive methods (ever use) in Greenlandic and Danish women 20–39 years of age.

difference in incidence rates cannot be explained by differences in cervical cancer screening activity between the 2 areas.

As part of a comprehensive study of women chosen at random from the populations of Nuuk, Greenland, and Nykøbing Falster, Denmark, information was obtained on risk factors for cervical cancer, as well as infections with human papillomavirus, type 16/18 and 6/11, and with herpes simplex virus, type 2 (Kjaer *et al.*, 1988). In the present study we find substantial differences between Greenlandic and Danish women with regard to marital status, sexual habits, smoking and contraceptive use. Most women in Denmark are married, whereas the most prevailing habit in Greenland is cohabitation (Table I). Greenlandic women are much younger at first intercourse (Table II, Fig. 1), they report many more sexual partners (Table II, Fig. 2), and they use either non-barrier contraceptives (OC, IUD) or none at all, more frequently than Danish women (Table II).

It is not clear whether age at first intercourse and number of sexual partners act as 2 independent risk factors for cervical cancer. Independence has been found in some case-control studies after controlling for potential confounding by other factors (Clarke *et al.*, 1985; La Vecchia *et al.*, 1986; Brinton *et al.*, 1987). By contrast, Reeves *et al.* (1985) found an independent association for carcinoma *in situ* only, and not for carcinoma *in situ* combined with invasive cervical cancer. Harris *et al.* (1980) reported that the effect of age at first intercourse disappeared after adjustment for life-time sexual partners.

In our study, we also find a clear association between early sexual debut and many partners (Table III). Independently of the number of sexual partners, Greenlandic women have a significantly earlier onset of sexual life than Danish women (Table III), and more partners, regardless of age at first intercourse.

A protective effect of barrier contraceptive methods (condom, diaphragm) against cervical cancer has been reported repeatedly (Terris and Oalmann, 1960; Vessey *et al.*, 1976; Wright *et al.*, 1978; Harris *et al.*, 1980; Fasal *et al.*, 1981; Peters *et al.*, 1986), and persists after adjustment for potential confounding factors (Wright *et al.*, 1978; Peters *et al.*, 1986). Thus, in the literature the use of condoms is considered as a barrier method, but strictly speaking the protective value of this kind of contraception is only high if the condom is worn throughout the entire coitus and not only in the last part of it. Presumably this matter will be very hard to clarify. In Greenland some 80% of all the women aged 20–39 have never used barrier contraceptives during any part of their sexually active period of life, compared with some 40% in Denmark.

The role of OC is more equivocal. Some studies have found a positive association between OC and invasive cervical cancer after taking different confounding factors into consideration (WHO, 1985; La Vecchia *et al.*, 1986; Brinton *et al.*, 1986*a*) and with *in situ* cancer or dysplasia (Harris *et al.*, 1980; Vessey *et al.*, 1983). Others have not been able to confirm this association either in invasive cancers (Peters *et al.*, 1986; Irwin *et al.*, 1988) or in dysplasia (Clark *et al.*, 1985). In the Greenland/Denmark comparison, the high-incidence area contains a lower proportion of women who have ever used OC and of long-term users.

We find significantly different proportions of women having never used any contraception in Greenland (13.7%) and in Denmark (3.3%). In all probability some of the difference may be explained by a higher prevalence of sterility caused by multiple genital infections in Greenland.

It has been suggested that smoking may be a risk factor for cervical cancer (Winkelstein *et al.*, 1977). Most case-control studies and cohort studies have reported a relationship between smoking and *in situ* and invasive cervical cancer (Cederlöf *et al.*, 1975; Wigle *et al.*, 1980; Harris *et al.*, 1980; Marshall *et al.*, 1983; Lyon *et al.*, 1983; Trevathan *et al.*, 1983; Clarke *et al.*, 1985; Greenberg *et al.*, 1985; Brinton *et al.*, 1986*b*; Peters *et al.*, 1986; La Vecchia *et al.*, 1986). In several of these studies the relative risk remains elevated after adjustment for related risk factors such as number of sexual partners and age at first intercourse.

In our cross-sectional study, we find a higher prevalence of current smokers in the high-incidence area for cervical cancer (Greenland), in comparison with the low-incidence area (Denmark). Although female smokers in Denmark smoke more than their Greenlandic counterparts, the average cigarette consumption in the Greenlandic population is higher than in Denmark.

The incidence of cancer of the cervix has been shown to correlate with the distribution of cancers related to smoking (Winkelstein *et al.*, 1977). Greenlandic women also have one of the highest incidence rates of lung cancer on record in the world [1975–83: 21.4 per 100,000 person/years (World Standard)] (Nielsen and Hansen, 1982).

If we combine the high-risk criteria of: (1) first sexual intercourse before the age of 16; (2) more than 10 sexual partners; (3) unprotected cervix for more than 5 years of sexual life; and (4) more than 5 pack-years of smoking, altogether 25.8% of Greenlandic women fulfill these criteria compared with 5.1% of the women examined in Denmark ($p < 0.001$). In Greenland 83 out of 151 women (54.9%) of this high-risk group are positive for herpes simplex virus type-2 infection, while this is the case for 6 out of 34 women in Denmark (17.7%) ($p < 0.001$). A slightly higher proportion of women in the high-risk group are infected with human papillomavirus type 16/18 in Greenland (9.9%; 15/151), than in Denmark (5.9%; 2/34). The difference is not significant, however.

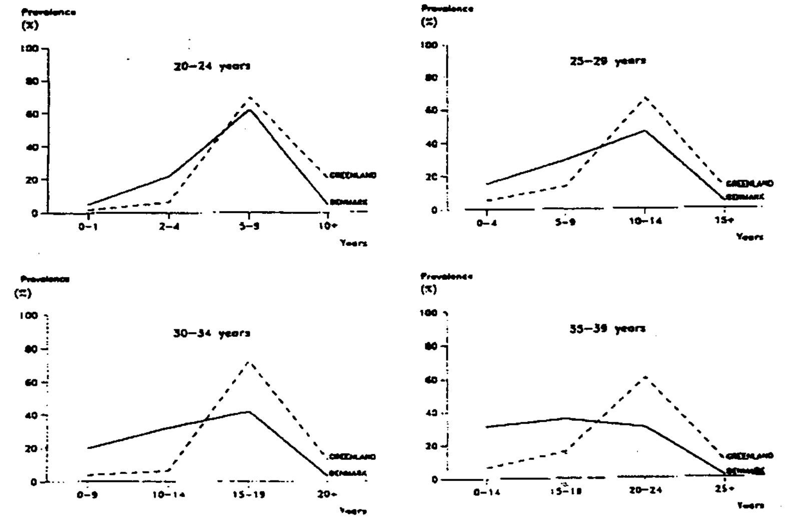

FIGURE 5 – Age-specific prevalence rates of numbers of sexually active years with unprotected cervix of Greenlandic and Danish women 20-39 years of age.

The theme of sexual behaviour is very private and perhaps even taboo for some people. In spite of this, we did not meet aversion to the request for information on sexual habits either in Greenland or in Denmark. Among the Greenlanders 1.4% did not wish to answer these questions specifically, whereas this applied to 1.1% of the Danish women. Before the start of the study we consulted local people in each area in order to make sure that the questions would fit into the norms, which presumably exist in the 2 different populations under study. The questions in the personal interview were purposely simple and even though we did not have any kind of control questions, both field teams had the general impression that women who actually took the trouble to participate also gave correct answers.

In summary, then, the Greenlandic population is characterized by a high prevalence of known risk factors for cervical cancer, in line with the observed high incidence of this tumour. This "high-risk profile" of Greenlandic women is in line with our previous observations of a significantly higher prevalence of antibodies to herpes simplex virus type 2 in that population compared with Denmark (Kjaer *et al*., 1988) and with the high rates of infections with gonorrhoea and syphilis (From, 1980). Our findings further underline the need for rigorous epidemiological studies of associations between cervical cancer and human papilloma virus infections, since we previously did not find the suspected risk factor for cervical cancer (human papillomavirus type 16/18) to be more prevalent in the high-risk Greenlandic population than in the Danish population (Kjaer *et al*., 1988).

TABLE IV – PREVALENCE RATES AND PREVALENCE ODDS RATIOS OF SMOKING HABITS AND LIFETIME USE OF CIGARETTES IN GREENLANDIC AND DANISH WOMEN 20-39 YEARS OF AGE

	Greenland		Denmark		Age-standardized odds ratio (Greenland/Denmark)	(95% CI)
	n	(%)	n	(%)		
Smoking						
Current	512	(87.4)	355	(53.6)	1.00	
Ex-smoker	41	(7.0)	73	(11.0)	0.40	(0.26–0.60)
Never	33	(5.6)	233	(35.3)	0.09	(0.06–0.13)
Lifetime use of cigarettes (pack-years)[1]						
0	33	(5.6)	233	(35.3)	0.10	(0.07–0.16)
<2	155	(26.5)	78	(11.8)	1.40	(1.00–2.00)
2–9	283	(48.3)	207	(31.3)	1.00	
>10	114	(19.5)	143	(21.6)	0.80	(0.58–1.11)

[1] One did not remember (Greenland).

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ATTACHMENT 3 John

ARTICLES

Epidemiologic Correlates of Cervical Neoplasia and Risk of Human Papillomavirus Infection in Asymptomatic Women in Brazil

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To investigate whether the epidemiologic correlates of cervical cancer are predictors of infection with genital human papillomavirus (HPV), we performed a prevalence survey in two metropolitan areas of Brazil, Recife and São Paulo. The data records of four randomly selected HPV-negative women were matched on the basis of age, clinic, and admission period with those of each of 136 patients with positive HPV DNA hybridizations. Anal intercourse [prevalence rate ratio (PRR) = 1.7] and current pregnancy (PRR = 2.3) were the only variables associated with HPV 6/11 infection (P < .10). Only the frequency of gynecologic consultations was associated (negatively) with risk of HPV 16/18 infection (*P* = .0175). Our data failed to provide evidence for the existence of shared risk factors for genital HPV infection and cervical cancer. The frequency of mixed HPV infections was 13 times higher than expected, a finding suggestive of the existence of additional determinants of HPV infection not akin to the general behavioral characteristics of women that are probed in the study. [J Natl Cancer Inst 81:332-340, 1989]

Epidemiologic studies have consistently shown that the main determinants of risk for cervical neoplasia are correlates of sexual activity. The characteristics generally identified in such investigations are (*a*) early onset of sexual activity, (*b*) multiple sex partners, and (*c*) promiscuity of the partner (*1-3*). In addition, other studies have suggested that wives of patients with penile cancer are at an increased risk of developing cervical cancer later in life (*4,5*). Such findings are further supported by results from population correlation studies, in which strong associations have been found between the development of cervical cancer and penile cancer with the use of mortality and morbidity data (*6,7*). These epidemiologic associations suggest a role for a sexually transmitted infectious agent in the etiology of cervical cancer.

Human papillomaviruses (HPVs) have been implicated as the most likely causal agents of cervical neoplasia, since much experimental and histopathologic evidence has been obtained in regard to the oncogenic potential of this group of viruses (*8,9*). HPV nucleic acid sequences have been found in a substantial proportion of specimens from cervical carcinomas occurring in different populations (*10*). Other investigations including surrogate control groups representative of asymptomatic women have demonstrated that, although HPV DNA sequences are also found in normal cervical epithelia, they are detected at rates that are much lower than those found in cervical cancer cases (*11-13*).

The above model of a single-agent causation for cervical cancer has two drawbacks. First, the mere statistical association between the HPV detection rate and the occurrence of disease is also consistent with another possible role for this group of viruses. On the basis of the hypothesis that abnormally proliferating epithelia would be more prone to infection by HPV, one would also observe a higher detection rate among women with cervical abnormalities than among normal controls. Secondly, cervical cancer appears to be a disease with a multifactorial pattern of occurrence, since other determinants (e.g., oral contraceptive use, parity, and tobacco smoking) have also consistently emerged as independent risk

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factors in epidemiologic investigations (*14*). Only prospective studies can disentangle the similarity of effects between the two models because, unlike cross-sectional or retrospective surveys, follow-up studies provide the correct time perspective needed for establishing causation. However, most prospective studies of HPV-infected women are in the initial stages; thus, their results are only preliminary and lack statistical power to provide conclusive evidence for the role of HPV as a causal agent for cervical cancer.

In the present investigation we propose an alternative study design for assessing the role of HPV in cervical neoplasia. Our investigation is based on the hypothesis that the sexual activity correlates of the disease are in reality determinants of genital infection with HPV. As such, these correlates should be directly measured in an epidemiologic study of behavioral predictors of the HPV prevalence rates in asymptomatic women.

Methods

Study Populations

Two Brazilian metropolitan areas were selected for the study: Recife and São Paulo. The capital of Pernambuco State, Recife is in Brazil's northeastern region and is considered to be a high-risk area for cervical cancer. The average annual incidence rate for this neoplasm (invasive disease) in Recife during the most recent survey period of 1976–1979 was 96.5 new cases per 100,000 women, age-adjusted by the world population (*15*). São Paulo, the capital of São Paulo State, is in southeastern Brazil and is considered to be an intermediate-risk area for cervical cancer, with an age-standardized incidence rate for 1978 of 35.1 (*16*).

Study subjects were selected by stratified random sampling of the adult female populations attending three family-planning and maternal and child health clinics, two in Recife [Instituto Materno-Infantil de Pernambuco (IMIP) and Hospital do Cancer de Pernambuco (HCP)] and the third in São Paulo [Hospital de Vila Nova Cachoeirinha (HVNC)]. The reasons given for attending the clinics included (*a*) routine medical examinations for women using contraceptive methods, (*b*) child immunization, and (*c*) general pediatric and gynecologic care. The nationwide health and social security system maintained by the Brazilian Government is billed directly for all health delivery services. Additional funding is provided under contracts by the municipal and state governments. These clinics maintain for their communities acive screening programs for cervical cancer. During the study period (April 1986 through April 1988), the combined biennial accrual for these clinics was 29,000 women. On the asis of this dynamic population, we selected 2,050 as the arget sample size, to allow sufficient statistical power to detect at least a 50% difference in HPV infection rate above the xpected prevalence level of 2% that was obtained during a retest phase conducted in São Paulo in 1986.

Informed consent was obtained from all patients. None of e selected patients refused to participate. A routine Papaicolaou cytology examination was done on all subjects. The otton-tipped swabs used for harvesting cervical cell specimens were immersed in phosphate-buffered saline (PBS) and refrigerated at 2–8 °C for, at most, 3 days before they were shipped in wet ice to the laboratory in São Paulo, where HPV DNA analyses were performed. After specimens were collected from the patients, the patients were subjected to a standardized, structured interview that lasted 30–40 minutes. The trained female interviewers elicited information on socioeconomic and demographic variables, smoking and alcohol drinking habits, personal hygiene practices, access to health care, reproductive history, and sexual practices. The interviewers were not aware of the study hypotheses or of any current or past cytologic results for the patients. Since the questionnaire dealt with sensitive information, the interviewers were asked to grade the responses of the patients on the basis of their willingness to cooperate in answering all questions.

HPV DNA Hybridization Analysis

Detection of HPV DNA sequences of subtypes 6, 11, 16, and 18 (provided by Professor Harald zur Hausen, German Cancer Research Center, Heidelberg, Federal Republic of Germany) was performed by the filter in situ hybridization method (*17*) with the following modifications. The cervical cell suspensions were centrifuged for 2 minutes at 1,500 *g*, resuspended in 1 mL of PBS, and counted in a hemocytometer to establish the number of cells delivered onto nitrocellulose filters (Millipore, 0.45-μm porosity, 25 mm in diameter). Cell-containing filters were overlaid on Whatman 3MM paper that had been soaked in denaturing solution (0.5 *N* NaOH, 1.5 *M* NaCl) for 5 minutes and then overlaid on Whatman paper that had been soaked in 1.5 *M* Tris-HCl and 0.5 *M* NaCl for 5 minutes. The filters were then air dried and baked at 80 °C for 2 hours. Only highly stringent conditions (18 °C below the melting temperature) were used for both hybridization and washing of the filters. The two halves of each filter were separately prehybridized in a solution containing 50% formamide, 5× Denhardt's solution (0.1% Ficoll, 0.1% polyvinylpyrrolidone, 0.1% bovine serum albumin), 5× SSPE [0.9 *M* sodium chloride, 50 m*M* sodium phosphate buffer (pH 7.4), 5 m*M* EDTA], 0.1% sodium dodecyl sulfate, and 100 μg of denatured salmon sperm DNA/mL at 42 °C for 12–18 hours and hybridized with radiolabeled HPV DNA sequences of subtypes 6, 11, 16, and 18. Probes were nick translated in the presence of ^{32}P-labeled deoxynucleotides to specific activities of 1–5 × 10^8 cpm/μg and added (combinations 6/11 and 16/18) to the hybridization mixture (5 × 10^6 cpm of ^{32}P-labeled DNA probe/mL). After 36–48 hours at 42 °C, filters were washed twice in 2× SSC (300 m*M* sodium chloride, 30 m*M* sodium citrate) and 0.1% sodium dodecyl sulfate at 68 °C for 30 minutes and exposed for 5 days at −70 °C to x-ray film (Kodak, X Omat, XK 1). Autoradiographs were read by a single observer (L. L. Villa), who was totally unaware of both the cytology results and the risk factor profiles of the patients. HPV DNA hybridization results were classified on the basis of the signal intensity of the autoradiographs into three categories: negative, borderline, and frankly positive. HPV-positive cell scrapings from cervical condylomata were used as positive controls in every hybridization batch.

Statistical Analysis

The total study sample accrued during the investigation was 2,618 patients. Excluded from the study were 253 patients whose cervical cell specimens could not be evaluated and an additional 35 patients whose questionnaires were judged to be of poor quality by the interviewers. For the remaining 2,330 women, HPV infection rates were calculated according to each study variable. The search for variables predictive of the likelihood of a positive HPV DNA result followed a two-step analysis. Initially, we estimated group-specific HPV prevalence rate ratios (PRRs) by computing crude and clinic-adjusted Mantel-Haenszel odds ratios and their 95% confidence intervals (CIs). Adjusted trend effects in the relationship between factor dose and magnitude of risk were evaluated by Mantel's extension to the Mantel-Haenszel method (*18*).

Because of the risk factor heterogeneity of the populations sampled in the study, a nested case–control analysis was subsequently performed to allow better control of confounding. The data records of four randomly selected patients with HPV-negative or borderline results were matched on the basis of clinic, 5-year age group, and trimester of admission with those of each of the 141 women with a frankly positive HPV result (either subtype). The process of computerized, random record linkage to generate the nested case–control matched sets eliminated five patients because fewer than four controls were available in their matching strata. The resulting case–control data set, consisting of 136 cases and 544 controls, was analyzed according to the subset determined by the HPV group: 89 HPV 6/11 cases with their corresponding 356 controls and 96 HPV 16/18 cases with their corresponding 384 controls. For each matched case–control subset, crude PRRs for all variables were computed by conditional logistic regression (*19,20*). The likelihood ratio chi-square statistics from each univariate matched analysis were used to build multivariate models containing all factors that were associated with risk of HPV infection at the 10% significance level. The most predictive models for each subset were then obtained by stepwise elimination of all variables not reaching the above significance level.

Results

None of the statistical correlates of a frankly positive HPV specimen were associated with the risk of having a borderline result (data not shown). If borderline results from autoradiographs represented for the most part true intermediate results, because of lower numbers of viral copies or lower frequencies of infected cells per specimen, their statistical correlates would be similar to those of frankly positive specimens. The number of epithelial cells per filter used in the hybridization was the most important determinant for our finding a borderline result. Frequencies of such results were two to four times higher among specimens containing >330,000 cells per filter than among specimens with lower cell counts. However, frankly positive specimens were only 1.2 times more frequently observed among lysates with higher numbers of cells. In addition, frequencies of HPV infection, as judged by frankly positive results, were much higher in the Recife clinics than in the São Paulo clinic, whereas the frequency of borderline results was higher in the clinic in São Paulo. Therefore, we considered borderline specimens as due mostly to background reactivity, and all subsequent analyses included these results among the clearly negative ones.

HPV infection rates according to HPV group and clinic are shown in table 1. Since the São Paulo population has many migrant groups from other Brazilian regions and, in particular, from the northeastern region, PRRs are presented both as crude estimates and after adjustment for the geographic origin of patients. Infection rates for both HPV groups were considerably higher in the Recife clinics than in the São Paulo clinic. There were no statistically significant differences in infection rates between the two Recife clinics, regardless of HPV group. The magnitude of the HPV 6/11 PRRs for study clinics was confounded by the geographic origin of the subjects. Geographically adjusted PRRs for HPV 6/11 were substantially higher than the crude estimates. The same was not observed for HPV 16/18, because adjusted estimates were not materially different from univariate PRRs (table 1).

Table 2 shows the frequencies of group-specific HPV infection according to selected socioeconomic and demographic factors. Because of the strong association seen with

Table 1. PRRs* and 95% CIs for HPV infection according to HPV group and study clinic

HPV group	Study clinic	Infection rate (%)	Crude analysis		Adjusted for geographic origin of patient	
			PRR	95% CI†	PRR	95% CI†
6/11	HVNC (São Paulo)	2.4	1.0	(ref)	1.0	(ref)
	IMIP (Recife)	5.5	2.4	1.4–4.0	4.4	1.5–10.4
	HCP (Recife)	4.7	2.0	1.0–3.8	3.9	1.2–11.1
	Both clinics (Recife)	5.2	2.3	1.4–3.8	4.1	1.4–8.7
16/18	HVNC (São Paulo)	2.0	1.0	(ref)	1.0	(ref)
	IMIP (Recife)	5.4	2.8	1.6–5.0	3.0	2.0–7.0
	HCP (Recife)	7.0	3.8	2.0–7.0	4.1	1.6–10.1
	Both clinics (Recife)	5.9	3.1	1.8–5.4	3.3	1.4–7.1

*Mantel-Haenszel odds ratio estimates.
†(ref) = reference category.

Table 2. Group-specific HPV infection rates (%) and PRRs* with 95% CIs according to selected socioeconomic, demographic, and related factors

Variable	No.†	HPV 6/11			HPV 16/18		
		%	PRR	95% CI‡	%	PRR	95% CI‡
Age (yr)							
≤25	561	3.9	1.0	(ref)	5.0	1.0	(ref)
26–32	631	4.1	1.2	0.6–2.2	4.4	0.9	0.5–1.7
33–41	571	4.4	1.3	0.7–2.4	4.0	0.8	0.5–1.5
≥42	567	3.7	1.1	0.5–2.0	3.5	0.7	0.4–1.4
Chi-square for trend (*P*):			0.001 (.9771)			1.735 (.1878)	
Race							
White	962	2.8	1.0	(ref)	2.6	1.0	(ref)
Mulatto	1,254	5.1	1.3	0.7–2.2	5.8	1.5	0.8–2.6
Black	103	2.9	1.0	0.2–3.6	1.0	0.3	0.0–2.2
Schooling (yr)							
≤4	1,191	4.1	1.0	(ref)	3.9	1.0	(ref)
5–8	941	3.4	1.0	0.6–1.6	4.1	1.4	0.9–2.2
≥9	198	6.6	1.6	0.8–3.1	7.1	1.8	0.9–3.5
Chi-square for trend (*P*):			0.961 (.3271)			4.287 (.0384)	
Monthly income (U.S. dollars)							
≤140	1,018	3.8	1.0	(ref)	5.1	1.0	(ref)
>140	1,036	3.9	1.5	0.9–2.5	3.6	1.1	0.7–1.8
Unknown	276	5.4	1.3	0.7–2.5	3.6	0.6	0.3–1.3
Marital status							
Never married	185	3.2	1.0	(ref)	7.0	1.0	(ref)
Ever married	2,145	4.1	1.4	0.6–3.5	4.0	0.6	0.3–1.2
Geographic origin							
Northern/northeastern region	1,685	4.5	1.0	(ref)	5.1	1.0	(ref)
Southern/southeastern region	625	3.0	2.1	0.7–5.1	2.1	1.0	0.4–2.7
Distance from clinic (km)							
1-10	1,256	3.2	1.0	(ref)	3.1	1.0	(ref)
≥11	979	4.8	0.9	0.5–1.7	5.3	1.0	0.6–1.7

*Mantel-Haenszel odds ratio estimates adjusted by study clinic.

†Missing values excluded from some analyses.

‡(ref) = reference category.

study clinic, PRRs are presented after we controlled for this variable. Group-specific infection rates and adjusted PRRs exhibited opposite directions of association with age, as measured in approximate quartiles of the distribution for this variable. However, neither the trends observed nor the level-specific PRRs reached statistical significance. Likewise, although mulattoes seemed to experience a 30%–50% increase in risk of HPV infection, the magnitude of the differences could be attributed to chance. Of the remaining variables, only years of schooling seemed to exert a risk effect for HPV 16/18. A trend test for this variable in regard to the association with HPV 16/18 was significant ($P = .0384$).

Similarly, table 3 displays equivalent information in regard to associations with selected variables for reproductive history. Most of these factors failed to be associated with risk of a positive HPV result, regardless of the HPV group. Patients who reported that they were pregnant during the interview seemed to experience a twofold higher risk of infection with HPV 6/11, a marginally significant association. Parity, a variable frequently associated with risk of cervical cancer, failed to correlate with the likelihood of HPV infection in either group.

The interviewer elicited information with respect to a number of health-related and personal hygiene practices (table 4). Of those, only the lifetime frequency of visits to a gynecologist was associated with risk of HPV infection, most notably for infection by HPV 16/18. Risk of infection was negatively associated with frequency of visits ($P = .0172$). None of the women with an altered Papanicolaou smear cytology (class III or higher) had a positive specimen for HPV 6/11. On the other hand, patients with abnormal smears had twice the risk of infection with HPV 16/18 than did women with cytology classes I and II. In neither case, however, did the association between cytology class and HPV infection risk reach statistical significance because of the small number of women with abnormal smears in the survey. Cigarette smoking or other forms of tobacco smoking were not predictors of the risk of HPV infection. Likewise, when cumulative exposure was calculated as number of pack-years of cigarette smoking, no dose–response relationship was found with risk of HPV infection (table 4).

Table 5 shows the association between risk of HPV infection and four surrogate measures of sexual activity and promiscuity. Most of these variables failed to exhibit important correlations with the likelihood of finding a positive HPV specimen of either viral group. Although women reporting more than five sex partners had a 30%–70% increase in risk of HPV infection when compared with the risk found in monogamous patients, the differences were not significant. Likewise, patients reporting having had their first intercourse

Table 3. Group-specific HPV infection rates (%) and PRRs* with 95% CIs according to selected reproductive history factors

Variable	No.†	HPV 6/11			HPV 16/18		
		%	PRR	95% CI‡	%	PRR	95% CI‡
Age at menarche (yr)							
≤12	840	4.0	1.0	(ref)	3.0	1.0	(ref)
>12	1,479	4.0	0.9	0.6–1.5	4.6	1.3	0.8–2.0
Parity							
0	242	5.8	1.0	(ref)	5.4	1.0	(ref)
1–2	819	3.5	0.7	0.3–1.4	4.8	1.0	0.5–1.9
≥3	1,268	4.0	0.7	0.4–1.4	3.7	0.7	0.4–1.4
Chi-square for trend (P):			0.287 (.5921)			1.921 (.1658)	
No. of abortions							
0	1,347	4.2	1.0	(ref)	4.4	1.0	(ref)
1	553	4.2	1.0	0.6–1.6	4.5	1.0	0.6–1.7
≥2	429	3.5	0.8	0.4–1.5	3.5	0.8	0.4–1.4
Chi-square for trend (P):			0.497 (.4810)			0.768 (.3807)	
Current pregnancy							
No	2,227	3.8	1.0	(ref)	4.2	1.0	(ref)
Yes	85	9.4	2.1	0.9–4.8	5.9	1.2	0.4–3.3
Use of oral contraceptives							
Never used	909	4.1	1.0	(ref)	4.4	1.0	(ref)
Ever used	1,421	4.0	1.1	0.7–1.7	4.2	1.1	0.7–1.7
Use of condoms							
Never used	1,983	4.0	1.0	(ref)	4.3	1.0	(ref)
Ever used	347	4.0	1.5	0.8–2.9	3.7	1.5	0.7–2.9
Use of intrauterine contraceptive device							
Never used	2,160	4.2	1.0	(ref)	4.3	1.0	(ref)
Ever used	170	2.4	0.7	0.2–2.1	3.5	1.2	0.5–3.1

*Mantel-Haenszel odds ratio estimates adjusted by study clinic.

†Missing values excluded from some analyses.

‡(ref) = reference category.

below the age of 16 were at 1.3 to 1.4 times higher risk of infection, but the confidence bounds for these estimates included the null value (unity). Conversely, lower risks were observed in patients with more active lifetime sexual activities after we controlled for the study clinic. However, as with the preceding analyses, no statistically important associations were seen. There were five virgins among the women surveyed. One of them was infected with both HPV 6/11 and HPV 16/18. The remaining four had no HPV infections.

The practice of anal intercourse was reported more frequently among women who had a positive HPV specimen. The clinic-adjusted PRR for this variable in regard to HPV 6/11 (1.9) was statistically significant at the 5% level.

The search for the most explanatory set of variables was based on the nested case–control subset, in which the matching criteria were maintained during the analysis by multiple logistic regression with the use of conditional maximum likelihood estimation. Table 6 shows the final models with predictive properties with respect to risk of HPV infection by groups 6/11 and 16/18. Both models were determined on the basis of conservative statistical criteria (10% significance level). The independent factors associated with risk of infection by HPV 6/11 included practice of anal intercourse and current pregnancy. For HPV 16/18, only one variable (i.e., frequency of visits to a gynecologist) exhibited a strong independent association with risk. When used as a single-term, ordinal variable, this variable caused the best improvement in fit. Additional independent explanatory effects were seen for number of cells per filter and age at first intercourse, both of which were used as dichotomous variables.

The dissimilarity between the above profiles of predictor variables prompted us to verify whether the distribution of group-specific infections was independent or exhibited a pattern that could reflect a joint mechanism favoring the occurrence of mixed (both HPV 6/11 and HPV 16/18) infections. Table 7 shows such an analysis as stratified by study clinic, the strongest determinant of the likelihood of finding a positive HPV specimen in this survey. The frequency of mixed infections was 13 times higher than that expected by chance alone, if one assumes independent distributions for group-specific infections. Higher observed frequencies were apparent for all three study clinics. The Recife clinics exhibited a similar pattern of joint distribution for HPV groups. The observed number of mixed infections in the São Paulo clinic was at an even higher level than that in the Recife clinics (ratio of observed to expected = 18).

Discussion

This study failed to provide strong evidence for the association between epidemiologic correlates of cervical cancer and risk of HPV infection of either subtype. With the exception of the study clinic and, by extension, the metropolitan area, determinants of risk for HPV infection with virus group 6/11 were not the same as those found for infection with group 16/18. Different subsets of predictor variables

Table 4. Group-specific HPV infection rates (%) and PRRs* with 95% CIs according to selected hygiene and health-related factors

Variable	No.†	HPV 6/11			HPV 16/18		
		%	PRR	95% CI‡	%	PRR	95% CI‡
Use of tampons							
Never used	2,307	4.0	1.0	(ref)	4.2	1.0	(ref)
Ever used	23	4.3	1.6	0.1–11.5	4.3	1.7	0.1–12.4
Vaginal douching							
Never	1,035	4.8	1.0	(ref)	4.8	1.0	(ref)
Ever	1,295	3.4	0.7	0.4–1.0	3.8	0.7	0.5–1.1
No. of visits to gynecologist							
0	192	7.8	1.0	(ref)	8.3	1.0	(ref)
1–2	491	3.9	0.6	0.3–1.4	5.5	0.8	0.4–1.7
≥3	1,637	3.7	0.6	0.3–1.1	3.4	0.6	0.3–1.1
Chi-square for trend (*P*):			2.068 (.1504)			5.673 (.0172)	
History of genital sores							
Never	2,072	3.9	1.0	(ref)	4.1	1.0	(ref)
Ever	240	5.4	1.2	0.6–2.2	5.4	1.1	0.6–2.0
Frequency of Papanicolaou smears							
1	723	4.8	1.0	(ref)	5.0	1.0	(ref)
2-4	1,008	3.8	0.8	0.5–1.4	4.5	1.1	0.7–1.7
≥5	599	3.5	0.9	0.5–1.6	3.0	0.8	0.4–1.5
Chi-square for trend (*P*):			0.226 (.6349)			0.339 (.5603)	
Smear class							
I–II	2,301	4.1	1.0	(ref)	4.2	1.0	(ref)
≥III	28	0.0	0.0	0.0–3.9	10.7	2.0	0.5–7.4
Smoking history							
Never smoked	1,173	3.8	1.0	(ref)	4.3	1.0	(ref)
Current smoker	806	4.8	1.4	0.9–2.2	4.2	1.0	0.6–1.6
Ex-smoker	350	3.1	0.8	0.4–1.6	4.0	0.9	0.4–1.6
Cumulative tobacco exposure (pack-years)							
<1	1,442	4.1	1.0	(ref)	4.6	1.0	(ref)
1–10	630	4.1	1.0	0.6–1.7	3.7	0.8	0.5–1.4
>10	239	3.3	0.9	0.4–2.0	2.5	0.6	0.2–1.4
Chi-square for trend (*P*):			0.042 (.8382)			0.451 (.5020)	

*Mantel-Haenszel odds ratio estimates adjusted by study clinic.

†Missing values excluded from some analyses.

‡(*ref*) = reference category.

were obtained with the use of conditional logistic regression on each group and its matched controls. Despite conflicting results for clinic-adjusted PRRs according to measures of sexual activity, age at first intercourse emerged as an explanatory variable for HPV 16/18 in the more controlled nested case–control analysis. However, both the magnitude of the PRR estimate for the latter variable and its statistical precision lacked strength of association. Other known correlates of cervical cancer risk (e.g., number of sex partners, parity, oral contraceptive use, and tobacco smoking) failed to exhibit any independent associations with infection by either HPV group. The strongest risk factor (protective effect) for HPV 16/18 was represented by the reported frequency of visits to a gynecologist. It is unlikely that this finding represents an indirect association due to differences in study populations, since controlling for age and clinic had been performed in the design and had been maintained during the analysis.

Besides study clinic and geographic origin, the only two predictors of risk of infection with HPV 6/11 were of marginal statistical significance. Practice of anal intercourse was positively associated with risk. We used this variable in the study to obtain an additional proxy variable for promiscuity. Although only a few women reported being pregnant during specimen collection and interview (85 patients, 3.7%), a relatively impressive proportion harbored HPV 6/11 DNA sequences in their cervices (9.4%). We had originally anticipated that such a finding would be a result of confounding by differences in fertility rates and age distributions between women in Recife and São Paulo, which could have influenced the proportion of pregnant women among the survey subjects. However, further adjustment by study clinic and the analysis of the finely matched strata of the case–control subset revealed an independent explanatory risk effect for current pregnancy. A similar finding has been shown in a previous study (*21*).

The number of epithelial cells used in the assay exerted a nonnegligible effect on the likelihood of finding a positive HPV 16/18 specimen. A preliminary exploratory analysis of factors associated with the likelihood of obtaining borderline and frankly positive specimens revealed a strong role for the cell counts only with respect to borderline hybridizations. Therefore, in the interest of conservative interpretation and because borderline results did not differ in frequency among the study clinics, we decided to use only frankly positive specimens as equating with HPV infection (*22*).

A striking finding from the present study was represented by the marked joint distribution of group-specific infections. Since the sets of predictor variables found for the two HPV groups were distinct, we expected that study clinic or city alone could explain the high number of mixed infections seen in this investigation. Prevalence rates had been much higher in the Recife clinics; thus, one could speculate that the observed number of combined infections was caused by a "concentration" effect that was due to the higher risk experienced by women from Recife. This situation was not the case, however, since the ratio of observed to expected cases was abnormally high for all clinics. This finding suggests the existence of a strong common determinant for group-specific HPV infections.

The choice of methods for viral DNA detection is far from resolved (*23*). The filter in situ hybridization method is con-

Table 5. Group-specific HPV infection rates (%) and PRRs* with 95% CIs according to selected sexual activity variables

Variable	No.†	HPV 6/11			HPV 16/18		
		%	PRR	95% CI‡	%	PRR	95% CI‡
Age at first sexual intercourse (yr)							
≥20	750	4.0	1.0	(ref)	3.6	1.0	(ref)
16–19	1,079	3.3	0.8	0.5–1.4	4.0	1.1	0.7–1.9
≤15	491	5.3	1.3	0.7–2.3	5.3	1.4	0.8–2.5
Chi-square for trend (*P*):			0.572 (.4494)			0.920 (.3375)	
No. of sex partners							
1	1,441	4.0	1.0	(ref)	4.0	1.0	(ref)
2–5	781	3.8	1.0	0.6–1.5	4.6	1.2	0.7–1.8
≥6	94	6.4	1.7	0.6–4.1	5.3	1.3	0.5–3.6
Chi-square for trend (*P*):			0.261 (.6094)			0.490 (.4837)	
Lifetime occasions of sexual intercourse							
≤410	428	4.7	1.0	(ref)	5.6	1.0	(ref)
411–900	490	3.5	0.7	0.4–1.5	4.7	0.8	0.4–1.5
901–1,560	489	3.3	0.7	0.3–1.4	3.3	0.5	0.3–1.1
1,561–2,600	438	4.3	0.9	0.5–1.8	3.2	0.5	0.3–1.1
≥2,601	450	4.0	0.8	0.4–1.6	3.8	0.6	0.3–1.2
Chi-square for trend (*P*):			0.021 (.8849)			1.989 (.1584)	
Practice of anal intercourse							
Never practiced	1,954	3.5	1.0	(ref)	3.9	1.0	(ref)
Ever practiced	366	6.3	1.9	1.1–3.1	5.2	1.4	0.8–2.3

*Mantel-Haenszel odds ratio estimates adjusted by study clinic.

†Virgins and unknowns excluded.

‡(ref) = reference category.

Table 6. Variables most associated with the risk of HPV infection in 680 cytologic specimens (136 cases and 544 controls)*

Variable	Relative risk	95% CI	*P* value†
HPV 6/11 (89 cases and 356 controls)			
Anal intercourse (ever vs. never)	1.69	0.95–3.01	.0795
Current pregnancy (yes vs. no)	2.31	0.88–6.08	.0877
HPV 16/18 (96 cases and 384 controls)			
Frequency of visits to gynecologist (0, 1–2, ≥3)	0.65	0.45–0.93	.0175
No. of cells per filter (×1,000) (>200 vs. ≤200)	1.58	0.96–2.61	.0675
Age at first intercourse (≤15 yr vs. >15 yr)	1.67	0.99–2.83	.0817

*Matched on clinic, 5-yr age group, and trimester of admission. Results obtained by conditional logistic regression with the use of stepwise elimination of terms based on a significance level of 10%.

†Likelihood ratio chi-square between current model and a reduced one excluding the variable.

Table 7. Frequencies of HPV-infected women according to HPV group and study clinic

Study clinic	No. of women not infected with HPV*	No. of women infected with			Infection with both HPV 6/11 and HPV 16/18	
		HPV 6/11 only	HPV 16/18 only	Both HPV 6/11 and HPV 16/18	Expected	Ratio† of observed to expected
HVNC (São Paulo)	935	14	10	9	0.5	18.0
IMIP (Recife)	860	23	22	28	2.7	10.4
HCP (Recife)	394	5	15	15	1.4	10.7
All clinics	2,189	42	47	52	4.0	13.0

*Based on the subtypes used in the study.

†Ratio of actual frequency of combined infections (HPV 6/11 and HPV 16/18) to that expected by chance alone.

sidered to be less sensitive than the Southern blot analysis according to some studies (22). Nevertheless, under stringent conditions, the filter in situ hybridization technique has a specificity comparable to that of the latter method and is more conveniently adapted to population surveys. A recent study has attributed comparable sensitivity and specificity to the two methods (24). However, it is still premature for one to judge the diagnostic performance of the two major methods from isolated studies while many different technical variants are being practiced, as reported in the literature. Case ascertainment in the present survey relied exclusively on the filter in situ hybridization test, which could have represented a possible source of error. Important random misclassification of cases and controls would have resulted if the number of false-positive and -negative hybridizations had reached a substantial proportion among all study subjects. In this situation, the PRR estimates would have been biased toward the null value. Because most of our study's findings were based on the absence or weakness of associations between epidemiologic correlates of cervical cancer and risk of HPV nfection, one cannot immediately rule out the hypothesis of andom misclassification. However, the sensitivity of the filter in situ hybridization assay by the present set of results may be judged as comparable to that of other prevalence studies (22,25). Likewise, if a substantial number of random misclassifications had occurred, the proportions of mixed inections as analyzed above would have fluctuated markedly and a smaller frequency of co-positive hybridizations would have been observed. In addition, a high degree of specificity s contributed by the high stringency conditions with which ell-containing filters were hybridized with the viral probes.

Lack of associations with most study variables would also have emerged if there had been random misclassification of exposure levels for factors correlated with cervical cancer. If his problem had occurred, one would fail to observe associtions between key study variables and risk of an abnormal ervical cytology. However, despite the low frequency of the atter results (28 patients), we found significant ($P < .05$) associations (data not shown) for schooling and frequency of Papanicolaou smears (negative) as well as for number of lifetime occasions of sexual intercourse (positive). In addition, marginal associations were seen for parity (positive) and family income (negative).

The evidence suggesting an etiologic role for certain subypes of HPV in regard to cervical malignancy is more conrete than that for most other microbial agents, such as *Trichmonas*, *Chlamydia*, cytomegalovirus, and herpes simplex irus. Strong support for the oncogenic role of HPV in the enital tract has stemmed mostly from four types of observaions: (*a*) most genital cancers harbor HPV DNA sequences; b) the physical state of the viral DNA differs (i.e., viral DNA is mostly integrated in invasive tumors and extrachroosomal in benign and premalignant lesions) (26,27); (*c*) anscriptionally active viral genomes are frequently found in cervical tumors and their cell lines maintained in culure (28,29); and (*d*) malignant transformation is obtained hen viral DNA is transfected into mammalian cells in culure (30,31). However, recent reports have challenged the nsistency of some of these lines of evidence. In different populations, HPV DNA has been found in surprisingly high frequency among women with normal cervices (32). In addition, some studies have shown that the within-specimen distribution of the viral DNA and its transcriptional activity in cervical tumors exhibit a "patchy" pattern of occurrence (33,34).

With the exception of the above fourth line of evidence, all other observations are also consistent with an additional activity that could explain the association between HPV and cervical cancer. HPVs are a group of viruses with strong epitheliotropic properties; thus, by merely claiming such properties, one could accommodate the findings of their statistical association with abnormal cervical proliferation. The physical state and expression differences found between advanced and precursor lesions could also be a consequence of long-lasting infection by the virus. Another tenable model would accommodate both hypotheses by the assumption that viral infection may not represent a necessary and sufficient single etiologic component. Neoplastic changes in the cervix could begin and progress without the presence of either the HPV DNA or its transcriptional activity, but it would be plausible for one to assume that the virus has an important role as promoter (27). The proper distinction among these etiologic models must be obtained through sensible epidemiologic study designs. Unfortunately, most of the clinico-epidemiologic investigations of HPV and genital cancer have been plagued by a number of problems affecting their validity (23).

In the present investigation, we provided results from an alternative epidemiologic study design. Although the difficulty resides in researchers obtaining an identifiable time perspective in regard to appearance of viral infection and onset of malignancy, it is simple to obtain histories of behavioral and other characteristics of women that would be conducive to risk of infection. As such, our study was based on the assumption that HPV infection is in the causal pathway represented by female sexual activity correlates and cervical cancer.

The prevalence survey design was selected for our study because of its inherent advantage in allowing an a posteriori definition for the control group. This advantage eliminated possible biases with self-selection and lack of comparability of control patients. Another advantage of the nested case–control approach of analysis is that the controls can be matched to cases on the basis of factors that could potentially confound the interpretation of results. Matching criteria controlled for characteristics that could fluctuate over time (e.g., diagnostic ascertainment quality and specimen collection technique) and factors that are associated with the balance of putative risk factors for the disease (e.g., age and clinic).

We found higher HPV infection rates in Recife than in São Paulo, a finding in agreement with the observed differences in cervical cancer incidence rates between the two cities. However, this observation is purely ecologic and should not be construed as evidence for an association between HPV infection and cervical neoplasia. In fact, the bulk of the results generated by the present study suggests that HPV infection and cervical cancer are elicited by different risk factor profiles. Our findings regarding a higher than expected frequency of infections with both HPV groups (6/11 and 16/18) are also suggestive of the existence of additional common determinants for the risk of HPV infection. These determinants are not akin to the general behavioral characteristics of women that are typically probed in epidemiologic studies of cervical cancer.

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CDC RESPONSES TO QUESTIONS ON HPV AND CERVICAL CANCER FROM THE SUBCOMMITTEE ON HEALTH AND ENVIRONMENT

Question: 1. How does CDC decide for which sexually transmitted diseases it will compile surveillance data? Please provide a list of all sexually transmitted diseases for which CDC currently recommends that states compile data. Please provide the number of female deaths per year associated with the sexually transmitted diseases for which the CDC has surveillance data.

Answer: Notifiable diseases are determined by individual state laws, not by CDC. All reports of notifiable diseases to CDC are voluntary on the part of the states. Generally, CDC compiles surveillance data for sexually transmitted diseases that are notifiable in all 50 states (gonorrhea, syphilis, chancroid; chlamydia is reported in 49 states). CDC also monitors non-notifiable diseases such as genital herpes by conducting special prevalence studies in the U.S. population (e.g., the National Health and Nutrition Examination Survey) and in smaller subpopulations. These kinds of special studies define the disease burden in the U.S. and often establish the need for diseases to become notifiable at the state level.

According to a CDC study, there were 2,665 female deaths attributable to HIV, 99 to syphilis, and 3 to gonorrhea in 1992, the latest year for which comparable data are available (Ebrahim et al. Mortality related to STD in US women, 1973 through 1992. American Journal of Public Health 1997;87:938-944).

Question: 2A. Can the human papillomavirus ("HPV") be transmitted in non-sexual manner? *2B.* How can someone prevent its transmission?

Answer: A. Of the approximately 80 different types of HPV infection, about 50 are considered to be non-genital (i.e., almost never occur on genital skin) and are almost always transmitted in a non-sexual manner. Of the approximately 30 genital types, sexual intercourse appears to be the predominant route of transmission. However, it has also been suggested that in rare cases, infection of genital skin with HPV can result from vertical transmission (mother-to-child during vaginal delivery); "autoinoculation" of non-genital types of HPV to the genital skin from another body part (such as the hand); inoculation through casual contact with genital skin, such as bathing; or transmission by inanimate objects (such as towels). (Cason, 1995).

B. The most reliable means of preventing sexual transmission of genital HPV infection is likely to be abstinence, although, as noted above, non-sexual routes of transmission are possible. Other means of protection are more uncertain. The protection provided by condoms has been difficult to evaluate because current laboratory tests for HPV infection cannot determine whether an infection is new or acquired months or even years before. Latex condoms should provide protection if they cover the infected genital skin and if used consistently and correctly. The greater surface area of the female condom may provide even greater protection, although there are no data evaluating its effectiveness in this regard. Finally, microbicides under development may provide some protective benefit (Howett, 1999). The most promising approach for prevention of transmission will be the development of preventive vaccines. Carefully designed studies of all of these transmission prevention approaches will be important in designing more effective prevention strategies.

Question: 3A. Can the body eliminate HPV from its system? *3B.* What can be done for those people who have compromised immune systems?

Answer: A. Whether the body can eliminate HPV from its system, that is, totally eradicate it (which is what we think happens with respiratory viruses such as those which cause influenza or the common cold) has been difficult to determine. There is good evidence that in most people genital HPV infections become "undetectable" by even highly sensitive lab tests for detection of HPV DNA (such as PCR) over the course of a few months to a few years (Ho, 1998), and it appears that such people do not have an increased risk for development of dysplasia or cancer. On the other hand, people with persistently detectable HPV infection appear to be at higher risk for dysplasia, and probably also cancer.

Evidence which suggests that undetectable HPV infection might not be totally eradicated from the body comes from patients with compromised immune systems, such as those taking immunosuppressive medication after an organ transplant or those with HIV infection, in whom the rate of detectable HPV infection is much higher than it is in patients whose immune systems are normal (Sun, 1997; Halpert, 1986). While some of this difference could be attributed to a greater risk of acquiring a new HPV infection among those with greater sexual risks (such as those with sexually acquired HIV), the fact that the rate of detectable HPV increases directly with declining immune function, even among patients who become less sexually active due to their illness, suggests that at least some or most of this excess level of infection is due to reactivation of previously undetectable infection which was quiescent but not completely eradicated. The similar experience in older, and probably less sexually active transplant recipients, is also consistent with such a process.

B. For those with compromised immune systems, there are two current approaches to help them with potential HPV-related problems. The first is to be sure that women undergo Pap smear screening at recommended intervals (which for those with HIV infection is every 6 months for a year and then annually thereafter), as well as follow-up evaluation of any abnormalities, in order to prevent what may be an increased risk of cervical cancer. The second approach is to attempt to maintain and improve immune function if possible, such as with the use of highly active antiretroviral therapy in those with HIV infection, which has the potential to reduce the risk of HPV-associated dysplasia and cancer. Better studies are needed to help develop management approaches in people with compromised immune systems.

Question: 4. On January 12, 1999, Chairman Bliley sent a letter to the National Cancer Institute (NCI) on women's health issues, including cervical cancer. In response to that letter, NCI estimated the number of Americans with HPV to be 24 million. In testimony before this committee on March 16, 1999, you indicated that number is 45 million. Can you explain the discrepancy in numbers?

Answer: Because HPV infection is not diagnosed in most people who are infected and because there are no systems in place for reporting of HPV infection, assessment of prevalence can only be based on very general estimates. This issue is further complicated, as noted in the answer to Question 3, by the problem that it has not yet been determined whether infection no longer measurable by sensitive HPV DNA detection tests such as PCR have truly resolved or are simply quiescent but still present, which is the assumption made for other viral sexually transmitted diseases such as genital herpes.

With these complexities in mind, there have been several attempts to quantify the prevalence of what are considered to be active genital HPV infections. Prior to 1999, the most widely quoted estimate of active genital HPV infection was 24 million (IOM Report). As of 1999, new revised estimates for the prevalence of the various sexually transmitted diseases stated that "a conservative estimate of the prevalence of productive HPV (persons with active shedding of HPV DNA) is approximately 20 million" (Cates, 1999).

Estimates of viral sexually transmitted disease prevalence based on serologic studies (assessments based on the presence of antibody in the blood) are much higher. For genital herpes, the estimated prevalence is 45 million, and the number of cases of genital HPV infection appears to be at least as great as the number of cases of genital herpes. However, estimates of the number of people who have been infected (and might still be at least quiescently infected) with genital HPV based on serologic studies are as high as 100 million (Koutsky, 1997).

Clearly, a very large number of Americans have genital HPV infection, and better studies are needed to further refine these estimates.

Question: 5. NCI stated that "additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted." CDC's testimony stated "Several studies have shown condoms to provide some protection against cervical cancer." Please explain the difference in conclusions and also cite the studies to which you refer.

Answer: NCI statement refers to genital HPV infection, not cervical cancer. Two case-control studies documented a strong protective effect of condom use and cervical cancer. In one study in Utah, condom use was associated with a lower risk of cervical cancer in women who had more than one sex partner; these women had a 47% lower risk of cervical cancer compared to women who did not use condoms (Slattery ML, Overall JC, Abbott et al: Sexual activity, contraception, genital infections, and cervical cancer: support for a sexually transmitted disease hypothesis. American Journal of Epidemiology 1989;130:248-258). In another study conducted in Los Angeles, women who used condoms for 2-9 years had a 50% reduction in risk of cervical cancer, and those who used condoms for 10 or more years had a 60% reduction in risk, compared to women who had 0-2 years of condom use (Peters RK, Thomas D, Hagan DG, et al. Risk factors for invasive cervical cancer among Latinas and Non-Latinas in Los Angeles County. Journal of the National Cancer Institute 1986;77:1063-1077).

Other studies have not shown a protective effect (Hildeshim A, Brinton LA, Mallin K et al. Barrier and spermicidal contraceptive methods and risk of invasive cervical cancer. Epidemiology 1990; 1:226-272 and accompanying editorial Daling JR, Weiss NS: Are barrier methods protective against cervical cancer? Epidemiology 1990; 1:261-272.)

Question: 6. The CDC has identified risk factors, such as the human papillomavirus, in the development of cervical cancer. What work has CDC done to coordinate a Federal response to the prevention of cervical cancer? Specifically, what has CDC done to coordinate with the Department of Health and Human Services (HHS) Office of Population Affairs and the HHS Health Resources and Services Administration (HRSA) to alert women concerning the risk factors associated with cervical cancer? Who are the liaisons with CDC, HRSA, and the Office of Population Affairs? Has CDC coordinated activity with the Title V and Title XX programs within those agencies?

Answer: CDC has developed effective partnerships with HRSA and OPA on a local level. HRSA directs national health programs which improve the health of the nation by assuring quality health care to underserved, vulnerable and special-need populations. Under HRSA's direction, a nationwide network of 643 community and migrant health centers, and 144 primary care programs for the homeless and residents of public housing serve 8.1 million Americans each year. CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) contracts with many local HRSA health centers to provide services. Women eligible for CDC's program are referred to HRSA services for screening, diagnostic and treatment services as needed. To assist this effort, CDC and HRSA partnered on a successful conference, "Cancer Institute on Prevention and Treatment Strategies for Underserved Minority Populations," to focus effective outreach, prevention, screening, diagnosis, and cancer treatment services for underserved minority populations.

The OPA, within the Office of Public Health and Science of the DHHS, provides resources and policy advice on population, family planning, reproductive health, and adolescent pregnancy issues. OPA also administers two grant programs, the national Family Planning Program, authorized under Title X of the Public Health Service Act (PHSA) and the Adolescent Family Life Program, authorized under Title XX of the PHSA. In Fiscal year 1999, Title X Family Planning Clinics expect to serve nearly 5 million persons through a nationwide network of 4,600 clinics. Priority is given to persons from low-income families; services are provided at no cost to persons at or below the poverty level and on a sliding fee scale up to 250 percent of the poverty level. Many of CDC's NBCCEDP programs collaborate with Title X programs and share information with Title XX demonstration projects on a local level. Certain Breast and Cervical Cancer programs contract with family planning programs for screening services and some OPA's Title X programs refer women to NBCCEDP's contracted facilities for additional follow-up and diagnostic care when Pap testing detects abnormalities. These special partnerships are arranged on a local, State-by-State or program-by-program basis.

Finally, CDC's Division of Reproductive Health (DRH) is currently examining the effects of parity (the number of children born alive to a woman) and age at first birth on risk of invasive cervical cancer. CDC is using data from a population-based, case-control study of cervical cancer in Costa Rica collected between 1982 and 1984. Preliminary results suggest that risk of cervical cancer increased with increasing parity and decreased with increasing age at first birth.

The liaisons for the respective agencies are Nancy C. Lee, M.D., Division Director, CDC/NCCDPHP/DCPC; Marilyn H. Gaston, M.D., Associate Administrator, DHHS/HRSA/BPHC; and Thomas Kring, Deputy Director, DHHS/OS/OPHS/OPA.

Question: 7A. What is the amount of research dollars spent by CDC on HPV as compared to the virus that causes AIDS? *7B.* How many women die annually in the United States from cervical cancer? *7C.* How many women die annually in the United States from HIV-related illnesses?

Answer: A. During FY98, CDC spent approximately $1.25 million dollars for research on HPV and $41.356 million for research on HIV and AIDS.

B. In 1996, the latest year for which complete data is available, 4,552 women died of cervical cancer in the United States (CDC, National Center for Health Statistics, Deaths: Final Data 1996, National Vital Statistics Reports; Volume 47, Number 29).

C. In 1996, the latest year for which complete data is available, there were 5,853 HIV-related deaths among women in the United States (CDC, National Center for Health Statistics, Deaths: Final Data 1996, National Vital Statistics Reports; Volume 47, Number 29).

NATURAL HISTORY OF CERVICOVAGINAL PAPILLOMAVIRUS INFECTION IN YOUNG WOMEN

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ABSTRACT

Background Genital human papillomavirus (HPV) infection is highly prevalent in sexually active young women. However, precise risk factors for HPV infection and its incidence and duration are not well known.

Methods We followed 608 college women at six-month intervals for three years. At each visit, we collected information about lifestyle and sexual behavior and obtained cervicovaginal-lavage samples for the detection of HPV DNA by polymerase chain reaction and Southern blot hybridization. Pap smears were obtained annually.

Results The cumulative 36-month incidence of HPV infection was 43 percent (95 percent confidence interval, 36 to 49 percent). An increased risk of HPV infection was significantly associated with younger age, Hispanic ethnicity, black race, an increased number of vaginal-sex partners, high frequencies of vaginal sex and alcohol consumption, anal sex, and certain characteristics of partners (regular partners having an increased number of lifetime partners and not being in school). The median duration of new infections was 8 months (95 percent confidence interval, 7 to 10 months). The persistence of HPV for ≥6 months was related to older age, types of HPV associated with cervical cancer, and infection with multiple types of HPV but not with smoking. The risk of an abnormal Pap smear increased with persistent HPV infection, particularly with high-risk types (relative risk, 37.2; 95 percent confidence interval, 14.6 to 94.8).

Conclusions The incidence of HPV infection in sexually active young college women is high. The short duration of most HPV infections in these women suggests that the associated cervical dysplasia should be managed conservatively. (N Engl J Med 1998;338:423-8.)

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GENITAL infection with human papillomavirus (HPV) is one of the most common sexually transmitted diseases, its prevalence in young women ranging from 20 to 46 percent in various countries.[1-5] The effect of this infection on public health is compounded by the recognized causal relations between genital HPV infection and cervical dysplasia and cervical cancer.[6-8] Information about the natural history of HPV infection, however, is limited. Although there are numerous cross-sectional studies of its prevalence,[1,3,4,9] the probability of acquiring this infection and the risk factors for it are not known. Some studies have concluded that genital HPV infection is mainly transient, but they were based on small numbers and only two points in time.[10-14] Specific types of HPV are associated with cervical cancer,[15] but whether these high-risk types have natural histories that are different from those of other types not associated with cervical cancer is unknown. This prospective study was conducted to address these questions.

METHODS

Through campuswide advertisements, we recruited and enrolled 608 female students from a state university in New Brunswick, New Jersey. As reported previously, their mean (±SD) age was 20±3 years, and the racial and ethnic distribution was 57 percent white, 13 percent Hispanic, 12 percent black, and 18 percent other.[1] The prevalence of HPV infection at base line was 26 percent. The women were followed at six-month intervals for a maximum of three years. At each visit, a questionnaire on lifestyle and sexual behavior was completed, and cervicovaginal lavage was done.[16,17] A pelvic examination, including a Pap smear, was performed at base line and annually thereafter. The 608 women were seen a total of 2971 times (median, 5 visits each) during an average of 2.2 years of follow-up (maximum, 3.4 years). The median number of months between two consecutive follow-up visits was 6 (range, 3 to 24), and 89 percent of the follow-up visits were completed within 5 to 7 months after the previous visit. The study protocol was approved by the institutional review board of the Albert Einstein College of Medicine, and informed consent was obtained from all the women.

Detection of HPV DNA

Exfoliated cervicovaginal cells were obtained by lavage for determination and typing of HPV by the polymerase chain reaction (PCR) and Southern blot hybridization as previously described.[1,16,17] The HPV DNA fragments amplified by PCR that did not hybridize to any type-specific probes were considered to represent "uncharacterized" HPV types. A sample was considered positive for HPV if either the PCR or the Southern blot assay was positive, and negative if both assays were negative. No lavage samples were obtained during 14 of the 2971 visits, and the samples from another 63 visits were Southern blot–negative without PCR

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results; hence, the samples from 77 visits (3 percent) had indeterminate HPV results.

HPV types determined by PCR and Southern blot assay were combined into two groups: "high-risk" types known to be associated with cervical cancer (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and W13b) and all other types.[15] Sixteen of the 296 women (5 percent) in whom HPV DNA was ever detected had fluctuations in type — i.e., negativity for a specific type flanked by positivity. In the data analyses, these fluctuations were treated as loss of infection and then reinfection with that specific type.

Statistical Analysis

We estimated the cumulative probabilities of acquiring and losing an incident HPV infection and having an incident cytologic abnormality by the Kaplan–Meier method. The time of the event was estimated as the midpoint between visits. All P values presented are two-sided.

For the non–type-specific incidence of HPV, the results in the 399 women who were HPV-negative at base line and who had at least one follow-up visit were analyzed. Time-dependent proportional-hazards regression analysis was performed to identify independent risk factors for incident HPV infection. The incidence of a specific HPV type was analyzed in the women who at base line were either HPV-negative or positive for other types.

For the duration of HPV infection, data on the 175 women who had a new HPV-type–specific infection and at least one subsequent follow-up visit were analyzed. A woman was considered to have a persistent infection if at least one of the types continued to be detected at subsequent visits. For the duration of infection with a specific type of HPV, only the women with a new infection of that type were included. To identify risk factors for persistent HPV infection, a generalized linear regression model with a generalized estimating-equation approach was used.[18,19] The HPV results of every two consecutive visits of a woman were grouped as a pair, as previously described.[6] The outcome was classified as persistence when at least one of the types detected at the previous visit was detected at the next visit, and as resolution when none of the types from the previous visit were detected at the next visit. Because the majority of follow-up visits were completed within the 6-month intervals, this analytic approach defined persistent HPV infection as infection with the same type or types for ≥6 months.

For analysis of the incidence of squamous intraepithelial lesions, the 443 women whose HPV status was known and who had normal Pap smears at base line, excluding atypia, and at least one follow-up visit were included. The relation between HPV infection and the incidence of squamous intraepithelial lesions was examined by time-dependent proportional-hazards regression analysis.

RESULTS

Incidence of HPV

The cumulative 36-month incidence of HPV infection in the women who were HPV-negative at base line was 43 percent (95 percent confidence interval, 36 to 49 percent). The incidence tended to decrease with time; it was 20 percent in the first 12 months, as compared with 14 percent and 9 percent in the second and third 12-month periods, respectively.

The 20 types of HPV for which the 24-month cumulative incidences were ≥2 percent are listed in Table 1. The incidences of HPV types 51, 66, 16, PAP155, 6, 18, and 59 were the highest (≥4 percent). The mean (±SD) 24-month cumulative incidence of the 16 high-risk types of HPV was 3±2 percent, as compared with 2±2 percent among the 19 other HPV types, excluding the uncharacterized types (P=0.26).

TABLE 1. CUMULATIVE 24-MONTH INCIDENCE AND MEDIAN DURATION OF INFECTION WITH SPECIFIC TYPES OF HPV IN COLLEGE WOMEN.*

HPV TYPE	CUMULATIVE 24-MONTH INCIDENCE†	MEDIAN DURATION†	NO. WITH INFECTION/ NO. AT RISK	NO. IN WHOM INCIDENT INFECTION RESOLVED/ NO. AT RISK
	% (95% CI)	mo (95% CI)		
51‡	8 (6–11)	7 (6–12)	43/529	29/36
66	7 (5–10)	6 (6–7)	38/529	26/28
16‡	7 (4–9)	11 (7–12)	38/514	18/25
PAP155	7 (4–9)	7 (6–11)	35/526	25/28
6	5 (3–7)	6 (6–7)	29/531	22/23
18‡	4 (3–6)	12 (6–17)	22/525	11/17
59‡	4 (2–5)	6 (5–7)	19/527	14/14
53	3 (2–5)	8 (6–11)	21/521	16/19
61	3 (2–5)	15 (6–17)	17/529	10/13
52‡	3 (1–4)	7 (6–11)	15/531	11/13
39‡	3 (1–4)	6 (5–11)	13/530	11/11
73‡	3 (1–4)	11 (10–14)	15/527	9/12
58‡	3 (1–4)	6 (6–∞)§	13/528	6/9
PAP291	3 (1–4)	6 (6–7)	15/529	13/14
AE7	3 (1–4)	16 (11–22)	13/532	5/9
31‡	2 (1–4)	6 (6–13)	12/529	10/11
54	2 (1–4)	9 (6–20)	13/533	7/10
33‡	2 (1–4)	7 (6–8)	10/536	6/7
45‡	2 (1–4)	6 (5–12)	10/531	8/9
35‡	2 (1–3)	6 (5–7)	9/536	9/9

*The 20 types of HPV with the highest 24-month cumulative incidences (≥2 percent) are shown. Not shown are HPV types 11, 26, 32, 34, 40, 42, 55, 56, 67, 68, 70, AE2, AE6, AE8, and W13B, because their incidence was <2 percent. The total type-specific incidence is presented, although the incidence of a particular type tended to be lower among women who were HPV-negative at base line than among those who were HPV-positive with a different type. CI denotes confidence interval.

†The cumulative 24-month incidence and median duration of HPV infection were obtained by the Kaplan–Meier method. Confidence intervals for the median durations were derived with the use of the SAS statistical package[20] and by the methods described in Brookmeyer and Crowley.[21]

‡This type is high risk.

§The upper limit of the 95 percent confidence interval was not obtainable for HPV type 58.

An increased risk of incident HPV infection was associated with younger age, membership in a racial or ethnic minority group, and increased frequency of alcohol consumption (Table 2). The risk of HPV detection at a given visit was associated with the numbers of vaginal-sex partners both in the previous 6 months and in the previous 7 to 12 months. The women who had had at least one regular partner since the previous visit had an increased likelihood of acquiring an HPV infection if the partner was sexually promiscuous or not currently in school, or

TABLE 2. RISK FACTORS FOR INCIDENT HPV INFECTION IN COLLEGE WOMEN.

RISK FACTOR*	ADJUSTED RELATIVE RISK (95% CI)†	P VALUE
Time-independent variables		
Age (per additional yr)	0.9 (0.8–0.9)	0.001
Racial or ethnic group		
White, Asian, and others	1.0	
Hispanic	2.1 (1.2–3.7)	0.009
Black	4.4 (2.7–7.2)	<0.001
Time-dependent variables‡		
Frequency of alcohol consumption		
<1 time/mo	1.0	0.005§
1–3 times/mo	1.3 (0.9–2.1)	
≥4 times/mo	2.0 (1.2–3.1)	
No. of male vaginal-sex partners in previous 6 mo¶		
0–3	1.0	
≥4	3.6 (1.8–7.2)	<0.001
No. of male vaginal-sex partners in previous 7–12 mo¶		
0	1.0	<0.001§
1	1.7 (0.9–3.2)	
2–3	3.0 (1.6–5.8)	
≥4	4.2 (1.5–11.5)	
Had anal sex with any regular partners	1.6 (1.1–2.4)	0.03
Total frequency of vaginal sex with all regular partners‖		
<2–6 times/wk	1.0	
≥2–6 times/wk	1.5 (1.1–2.3)	0.02
No. of lifetime sexual partners of main regular partner**		
1	1.0	<0.001§
2–5	5.8 (2.1–16.0)	
≥6	10.1 (3.6–28.4)	
Main regular partner was currently in school**	0.6 (0.4–0.9)	0.01
Had at least one regular partner††	1.0 (0.5–1.9)	0.96

*The following variables were not significant in multivariate time-dependent proportional-hazards analysis: income; lifestyle; use of cigarettes, recreational drugs, and oral contraceptives; number of casual sex partners (sexual contact for <1 month); number of regular sex partners (≥1 month); number of new regular sex partners; frequency of oral sex and sex under the influence of alcohol or drugs; postcoital bleeding; sex during menstruation; use of vaginal douche; and use of condoms during vaginal sex.

†CI denotes confidence interval.

‡All time-dependent variables refer to the period since the previous visit unless otherwise specified.

§P value is for linear trend.

¶Number of sexual partners was normalized to a six-month period (i.e., the number of partners between two visits was divided by the number of months between two visits and multiplied by 6).

‖The frequency of vaginal sex since the last visit was coded as "none," "1–5 times," "1 time per month," "2–3 times per month," "1 time per week," "2–6 times per week," or "daily" in the questionnaire, and it was converted to the number of times per month by using the median frequency of each category. The total frequency of vaginal sex was the sum of the frequencies with all regular partners.

**If there were multiple regular partners, the most recent male partner with whom the woman had the most frequent sexual encounters and the longest relationship was considered to be the main regular partner.

††This is a dummy variable so that every woman, with or without a regular partner, could be entered into the regression model. All relative risks related to the characteristics of and sexual activities with the regular partner or partners were interpreted as risk estimates among women with at least one regular partner since the previous visit.[1,22]

if the woman and her partner were having anal sex or a high frequency of vaginal sex.

Duration of HPV Infection

The median duration of HPV infection was 8 months (95 percent confidence interval, 7 to 10). By 12 months after the incident infection, 70 percent of the women were no longer infected, and by 24 months only 9 percent continued to be infected. The five types of HPV associated with the longest median duration of infection were AE7, 61, 18, 16, and 73 (Table 1).

The risk factors for persistent HPV infection of ≥6 months were older age, infection with multiple types of HPV, and infection with a high-risk type at the previous visit (Table 3). A woman with a newly acquired HPV infection was unlikely to have the same infection six months later; the longer an infection persisted from previous visits the more likely it was to continue to persist. Cigarette smoking was protective against persistent infection.

Incidence of Squamous Intraepithelial Lesions

Thirty-one incident cases of squamous intraepithelial lesions were diagnosed by cytology, of which two were high-grade lesions. The women who had been HPV-positive at base line were three times as likely to have an incident squamous intraepithelial lesion as the HPV-negative women (95 percent confidence interval, two to seven times; $P<0.001$) (Fig. 1). All the women were HPV-positive when the lesions were detected, and 81 percent had also tested positive at the previous six-month visit. The risk of the development of squamous intraepithelial lesions was associated with having had an HPV infection for at least six months, particularly a persistent infection with a high-risk type (Table 4).

DISCUSSION

The average annual incidence of HPV infection in this cohort of college women was 14 percent. Including the 26 percent who were HPV-positive at base line, about 60 percent of the women were infected with HPV at some time during the three-year period of the study, revealing the high risk of exposure to HPV for both heterosexual men and women in a college environment.

A woman's risk of incident HPV infection was defined by her age, behavior, and the men with whom she associated sexually. Although the age range in this cohort was narrow, the older women had a lower risk of acquiring HPV infection than the younger women, perhaps because of acquired immunity to HPV from past exposure.[23] In addition to the transmission of HPV by vaginal sexual relations, the increased risk associated with anal sex or a high frequency of alcohol consumption may be a proxy for the risks associated with other forms of sexual be-

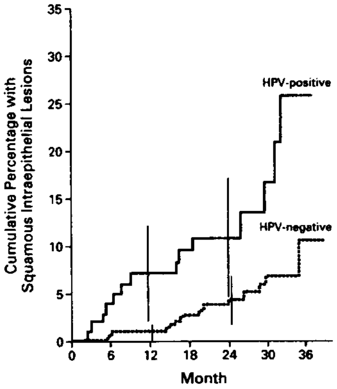
Table 3. Risk Factors for Persistence of HPV Infection for ≥6 Months in College Women.*

Risk Factor	Adjusted Odds Ratio (95% CI)	P Value
Age (per additional yr)	1.1 (1.1–1.2)	0.05
No. of cigarettes smoked/day since previous visit		
None	1.0	0.003†
≤5	0.8 (0.5–1.3)	
>5	0.3 (0.2–0.7)	
Status of HPV infection at previous visit‡		
New infection	1.0	
Already persistent for 6 mo	2.3 (1.4–3.8)	0.001
Already persistent for >6 mo	3.1 (1.8–5.6)	<0.001
Infection of unknown duration	1.4 (0.9–2.2)	0.19
Multiple types detected at previous visit	4.1 (2.7–6.3)	<0.001
High-risk types detected at previous visit	1.5 (1.1–2.2)	0.03

*Results were obtained from a time-dependent generalized linear regression model with a generalized estimating-equation approach.[18,19] CI denotes confidence interval.

†P value is for linear trend.

‡HPV results of two consecutive visits were grouped as a pair. An infection at the previous visit was classified as a new infection if the HPV types had not been detected at previous visits, as a continual type-specific persistent infection if at least one of the types had been detected six months or more than six months before, or as an infection of unknown duration if the most recent visit was the base-line visit or no information from previous visits was available.



No. of Women at Risk				
HPV-positive	102	83	68	21
HPV-negative	341	322	262	102

Figure 1. Cumulative Percentages of College Women with Incident Squamous Intraepithelial Lesions among Those Who Were HPV-Positive and HPV-Negative at Base Line.

Vertical bars represent 95 percent confidence intervals.

Table 4. Relative Risk for the Association between Continual HPV Infection and the Development of Squamous Intraepithelial Lesions.*

HPV Status	Relative Risk (95% CI)	P Value
HPV-negative at the previous or current visit	1.0	
HPV-positive at both visits†	20.9 (8.6–51.0)	<0.001
With different HPV types	14.7 (4.5–48.3)	<0.001
Non–high-risk types at current visit	9.6 (1.9–47.6)	0.006
High-risk types at current visit	22.2 (5.5–89.5)	<0.001
With the same HPV types	25.5 (10.2–63.7)	<0.001
Non–high-risk types	6.9 (1.4–34.1)	0.02
High-risk types	37.2 (14.6–94.8)	<0.001

*Results were obtained from univariate time-dependent proportional-hazards regression analysis. Continual HPV infection was determined by the HPV results at two consecutive visits — the current visit when a Pap smear was taken and the previous six-month visit. CI denotes confidence interval.

†Women who were HPV-positive at both visits were subclassified according to whether they had continual infection of different types or of the same type and whether high-risk types were involved. The relative-risk estimates were obtained from separate univariate analyses for each classification, with the women who were HPV-negative at one or both visits as the reference group.

havior that were not measured. The detection of incident HPV infection was associated with having four or more vaginal-sex partners in the previous six months. However, there was a direct relation between the detection of HPV infection and the number of vaginal-sex partners in the previous 7 to 12 months. These findings suggest a delay in the detection of HPV infection, perhaps related to the time required for the virus to replicate in cervicovaginal cells after infection.[3,24]

Several studies of prevalent HPV infection have concluded that HPV is mainly a transient infection.[2,10-12,14,25-27] The results of this study were similar for incident infections. Infection with high-risk types of HPV and older age were risk factors for persistent HPV infection.[12,25] The etiologic role of high-risk HPV types, as well as the peak incidence of cervical cancer in women more than 40 years old,[15,28] may be explained by the long duration of infection in older women infected with high-risk types. Persistent infection in turn may increase the risk for the development and persistence of squamous intraepithelial lesions, as shown in this and previous studies.[6,25] The association between persistent infection and multiple types of HPV suggests that women who have multiple types might have certain characteristics — e.g., deficient immune responses to HPV — that predispose them to persistent infection.[29] In fact, women who are immunosuppressed by infection with the human immunodeficiency virus are at increased risk for infection with multiple types of HPV.[30]

A woman was likely to lose her existing HPV infection if it was newly acquired, and the longer an infection persisted the more difficult it was to lose it. The probability of losing an incident HPV infection in the first 6-month period was 31 percent, and in the second 6-month period it was 39 percent; if an infection did not resolve in the first 12 months, the probability of its resolving in the third 6-month period dropped considerably, to 11 percent. This pattern is similar to the regression and persistence patterns of squamous intraepithelial lesions.[31,32]

Previous studies have implicated cigarette smoking as a risk factor for cervical cancer,[33,34] whereas it was protective against persistent HPV infection in this and another study.[12] The protective mechanism of smoking, whether it is a biologic or a confounding effect, is unknown.

Among the 35 types of HPV, the incidence of infection with the high-risk types was similar to the incidence with the other types. Nevertheless, types 16 and 18, which have the strongest association with cervical cancer,[15] were the only two types included in the top quartiles for both incidence and duration.

We found a relation between incident squamous intraepithelial lesions and continuous HPV infections (both type-specific and non–type-specific), which had been suggested in previous studies.[12,17] Whereas type-specific infections prolong the duration of squamous intraepithelial lesions,[6,25] repeated non–type-specific infections are associated with multiple episodes of squamous intraepithelial lesions, and both increase the chances that squamous intraepithelial lesions will be detected by periodic Pap smears.

Since some women could have acquired and lost an HPV infection between two six-month visits, this study may have underestimated the incidence and overestimated the duration of HPV infection. The trend of high incidence and short duration was therefore a conservative representation of the natural history of HPV infection in young women. However, we do not know whether these data apply to other populations, particularly older women.

Finally, clinicians who treat adolescent girls and young women should consider that HPV infection is mainly short-lived. Hence, the manifestation of HPV, particularly a low-grade squamous intraepithelial lesion, often undergoes spontaneous regression.[25,32,35] Moreover, whether aggressive surgical treatments for squamous intraepithelial lesions cure HPV infection or interrupt its transmission is not known. Current data on the natural history of HPV infection and its associated lesions suggest that conservative management, such as follow-up without ablative therapy, may be indicated in young women with low-grade squamous intraepithelial lesions associated with transient HPV infection.

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HUMAN PAPILLOMAVIRUS INFECTION IN WOMEN INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

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Abstract

Background Among women infected with the human immunodeficiency virus (HIV), there is a high prevalence of human papillomavirus (HPV) infections. However, little is known about the natural history of HPV infections in HIV-seropositive women, and persistent HPV infections may explain the increased risk of cervical squamous intraepithelial lesions and invasive cervical cancer in HIV-seropositive women.

Methods A total of 220 HIV-seropositive and 231 HIV-seronegative women in the New York City area were evaluated at two or more semiannual gynecologic examinations that included a Pap test, a test for HPV DNA, and colposcopy.

Results HPV DNA was detected at the initial examination in 56 percent of the HIV-seropositive and 31 percent of the HIV-seronegative women. After four examinations, the cumulative prevalence of HPV infection was 83 percent in the seropositive women and 62 percent in the seronegative women ($P<0.001$). Persistent HPV infections were found in 24 percent of the seropositive women but in only 4 percent of the seronegative women ($P<0.001$). Twenty percent of the seropositive women and 3 percent of the seronegative women had persistent infections with HPV-16–associated viral types (16, 31, 33, 35, or 58) or HPV-18–associated types (18 or 45) ($P<0.001$), which are most strongly associated with cervical cancer. The detection of HPV DNA in women with previously negative tests was not associated with sexual activity during the interval since the preceding examination.

Conclusions HIV-seropositive women have a high rate of persistent HPV infections with the types of HPV that are strongly associated with the development of high-grade squamous intraepithelial lesions and invasive cervical cancer. These persistent infections may explain the increased incidence of squamous intraepithelial lesions in HIV-seropositive women. (N Engl J Med 1997;337:1343-9.)

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INFECTION with the human immunodeficiency virus (HIV) is an important risk factor for human papillomavirus (HPV) infection and the development of HPV-associated lesions in the female genital tract. HPV DNA is 2 to 3 times as frequent in cervicovaginal-lavage specimens and almost 15 times as common in anal-swab specimens from HIV-seropositive women as in those from HIV-seronegative women.[1-6] In addition, HIV-seropositive women are about five times as likely as HIV-seronegative women to have squamous intraepithelial lesions, vulvovaginal condyloma acuminata, or anal intraepithelial neoplasia.[2-8] These findings suggest that HIV infection, HIV-associated immunosuppression, or both increase a woman's susceptibility to HPV infection or alter the natural history of preexisting HPV infection.

In HIV-seronegative women, the majority of anogenital HPV infections appear to be transient and self-limited.[9] Persistent infection with certain types of HPV, such as types 16, 18, 31, 33, 35, and 45, is thought to be necessary for the development of high-grade squamous intraepithelial lesions and cervical cancer.[10] Since HIV-seropositive women have an increased prevalence of squamous intraepithelial lesions, we suspect that these women are at increased risk for persistent HPV infection. However, most studies of anogenital HPV infections in HIV-seropositive women have been cross-sectional in design, and information about persistence and other aspects of the natural history of HPV infections in HIV-seropositive women is limited.

We conducted a prospective cohort study to determine the gynecologic characteristics associated with HIV infection. Women enrolled in this study underwent periodic HPV DNA testing, which enabled us to examine the effects of HIV infection and HIV-associated immunosuppression on the natural history of HPV infection.

METHODS

Study Design

A total of 424 HIV-seropositive and 381 HIV-seronegative women were recruited from the New York City area during the period from 1991 through 1993. The cohort is described in detail elsewhere.[1,7] In brief, women were recruited from clinics for sexually transmitted diseases, methadone maintenance, and HIV infection and from a study of HIV transmission in couples. Women were enrolled without regard to their risk of HPV infection or the clinical status of those infected with HIV. Informed consent was obtained from all the women enrolled, and the study was ap-

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proved by the institutional review boards of all the participating institutions.

At enrollment and at approximately six-month intervals thereafter, participants were interviewed and underwent a gynecologic examination that included a Pap test, a cervicovaginal lavage of 10 ml of phosphate-buffered saline (pH 7.4), and colposcopy with biopsy, if indicated. The current analysis is restricted to women without squamous intraepithelial lesions on the initial examination who had HPV tests at two or more examinations within a 12-month period. CD4+ T-lymphocyte counts within six months of each examination were obtained from clinic records or were obtained specifically for the study.

Detection of HPV DNA

Polymerase-chain-reaction (PCR) tests for HPV DNA were performed in a blinded fashion. Genomic DNA was isolated from cervicovaginal-lavage specimens[1] and amplified with the use of both the HPV L1 consensus primers of Manos et al., which amplify 25 types of anogenital HPV,[11] and type-specific E6 primers for HPV 16 and 18.[12] Samples were defined as positive for HPV DNA if they contained an ethidium bromide–stained band of the correct molecular weight after amplification and polyacrylamide-gel electrophoresis. The HPV type was determined by analysis of restriction-fragment–length polymorphism of the L1 PCR product.[13] In some cases, L1 PCR products could not be typed in this manner because too many types of HPV were present (in 3 percent of the samples) or there was too little amplification product (in 12 percent). Type-specific PCR for HPV types 16 and 18 detected considerably more infections with HPV types 16 and 18 than did the L1 PCR; 46 of 101 HPV-16 infections (46 percent) and 66 of 92 HPV-18 infections (72 percent) were detected only with the type-specific E6 primers. In contrast, only 24 of 101 HPV-16 infections (24 percent) and 7 of 92 HPV-18 infections (8 percent) were detected only with the L1 method.

Samples that were negative for HPV DNA were amplified with primers for the cKi-*ras* gene to ensure the integrity of the samples.[12] Samples in which neither HPV DNA nor the cKi-*ras* gene was amplified were considered inadequate for analysis and were excluded.

Statistical Analysis

The cumulative prevalence of HPV infection, defined as the cumulative probability of a positive test for HPV DNA at each sequential examination, was estimated with the use of the Kaplan–Meier method and the log-rank test.[14] Cumulative-prevalence curves were calculated according to the time to the first positive HPV test. In all Kaplan–Meier estimates, missing examinations were ignored.

Among women with detectable HPV DNA of any type at the initial examination, the probability of positive HPV tests at subsequent visits was estimated with the use of the Kaplan–Meier method and the log-rank test. These curves were calculated according to the time to the first negative HPV test. However, this approach does not differentiate among the specific types of HPV that are shed, and different types could be shed at different times. Therefore, we also examined persistent HPV infections, defined as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months. To compare the percentages of HIV-seropositive and HIV-seronegative women with persistent HPV infections, odds ratios and confidence intervals were calculated from logistic-regression models,[15] which were adjusted for the number of examinations by using indicator variables for two, three, four, five, or six or more examinations.

New HPV infections were analyzed among the women with no HPV detected on two or more consecutive examinations. The rate of new infections was defined as the number of newly detected HPV infections after two or more negative tests, divided by the number of examinations until an infection was detected or, if no infection was detected, the end of follow-up. For women with new HPV infections, information about sexual behavior during the interval between the examination at which HPV was first detected and the preceding examination was analyzed, and for women with no new infections, information about sexual practices during the interval between the last two examinations was analyzed.

RESULTS

Sociodemographic Characteristics of the Cohort

The cohort was composed of 424 HIV-seropositive and 381 HIV-seronegative women, of whom 220 HIV-seropositive and 231 HIV-seronegative women were included in the analysis. The two reasons for exclusion from the analysis were that cervical disease was detected at the initial examination (in 104 HIV-seropositive and 24 HIV-seronegative women) and that results were unavailable for two HPV tests within a 12-month interval during the study period (in 100 HIV-seropositive and 126 HIV-seronegative women). The women who were excluded from the analysis because they had fewer than two HPV tests did not differ significantly from those included in the analysis in age, race or ethnic group, education, marital status, or detection of HPV DNA at the initial examination ($P>0.05$ for all comparisons). However, women with two or more HPV tests were less likely to report a history of injection-drug use than those with fewer than two HPV tests (35 percent vs. 45 percent, $P=0.01$). Data from a total of 787 examinations in HIV-seropositive women and 721 in HIV-seronegative women were included in the analysis.

Among the women included in the analysis, those who were HIV-seropositive were similar to those who were HIV-seronegative in terms of age, race or ethnic group, education, and income. The mean age in both groups was 35 years. Forty percent of the seropositive women and 46 percent of the seronegative women were black ($P=0.13$), 45 percent of the seropositive women and 37 percent of the seronegative women had not completed high school ($P=0.07$), and 63 percent of each group had an annual income of less than $10,000. The seropositive and seronegative women were similar in terms of the reported number of lifetime sexual partners, condom use, and age at first sexual intercourse. However, there were some differences in other characteristics. For example, 27 percent of the seropositive women and 39 percent of the seronegative women were married ($P=0.03$), 24 percent of the seropositive women and 16 percent of the seronegative women reported a history of prostitution ($P=0.05$), and 40 percent of the seropositive women and 31 percent of the seronegative women reported sexual abstinence during the month before the initial examination ($P=0.04$).

Cumulative Prevalence of HPV DNA

HPV DNA was detected at the initial examination in 56 percent of the HIV-seropositive women and 31 percent of the HIV-seronegative women. The

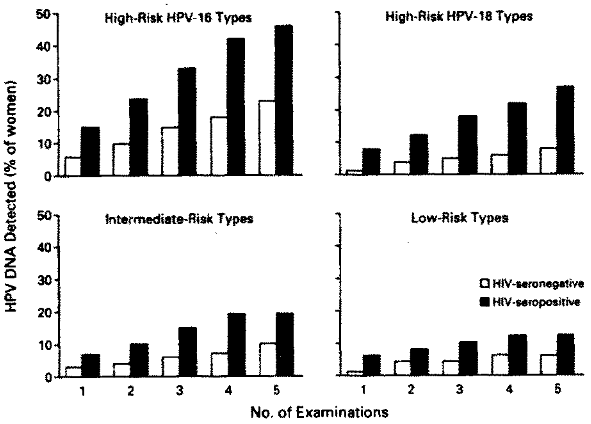

Figure 1. Kaplan–Meier Estimates of the Cumulative Prevalence of Types of HPV DNA in 220 HIV-Seropositive Women and 231 HIV-Seronegative Women.

The high-risk HPV-16–associated types were 16, 31, 33, 35, and 58, the high-risk HPV-18–associated types were 18 and 45; the intermediate-risk types were 51 and 53; and the low-risk types were 6, 11, 43, and 44.

cumulative prevalence of HPV DNA was higher in the HIV-seropositive women than in the HIV-seronegative women ($P<0.001$ by the log-rank test) and was inversely related to the CD4+ T-lymphocyte count. For example, the cumulative HPV prevalence after four examinations was 62 percent in the seronegative women, 74 percent in the seropositive women with CD4+ counts of 500 or higher per cubic millimeter, and 95 percent in the seropositive women with CD4+ counts that were below 500 per cubic millimeter.

The cumulative prevalence of specific phylogenetic groupings of HPV types was also analyzed.[16] Figure 1 shows the cumulative prevalence of the high-risk HPV-16–associated types (16, 31, 33, 35, and 58), the high-risk HPV-18–associated types (18 and 45), the intermediate-risk types (51 and 53), and the low-risk types (6, 11, 43, and 44). The cumulative prevalence of each group of HPV types was higher in the HIV-seropositive women ($P<0.001$ for both groups of high-risk types, $P=0.002$ for the intermediate-risk types, and $P=0.02$ for the low-risk types, by the log-rank test).

HPV-16–associated types and HPV-18–associated types are of particular interest because they are strongly associated with high-grade squamous intraepithelial lesions and invasive cancer in women in the general population. At the initial examination, the prevalence of HPV-16–associated types was 6 percent (95 percent confidence interval, 3 to 10 percent) in the seronegative women and 15 percent (95 percent confidence interval, 10 to 19 percent) in the seropositive women, and the prevalence of HPV-18–associated types was 1 percent (95 percent confidence interval, 0 to 3 percent) in the seronegative women and 7 percent (95 percent confidence interval, 3 to 10 percent) in the seropositive women. After four examinations, the cumulative prevalences in the seronegative and seropositive women were 18 percent (95 percent confidence interval, 13 to 24 percent) and 42 percent (95 percent confidence interval, 35 to 50 percent) for HPV-16–associated types and 6 percent (95 percent confidence interval, 3 to 9 percent) and 22 percent (95 percent confidence interval, 16 to 28 percent) for HPV-18–associated types, respectively.

Women who were positive for HPV at the initial examination frequently became negative for HPV during follow-up. Figure 2 shows the probability of detecting HPV DNA at subsequent examinations in women with detectable HPV at the initial examination. HIV-seropositive women were more likely than HIV-seronegative women to have positive HPV tests during subsequent examinations ($P<0.001$), and HIV-seropositive women with CD4+ T-lymphocyte counts of less than 500 per cubic millimeter were more likely than those with CD4+ counts of 500 or

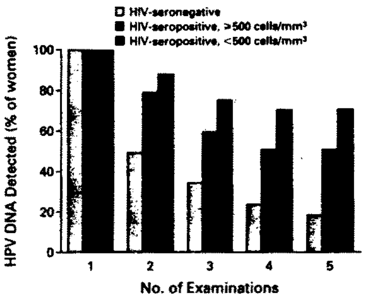

Figure 2. Kaplan–Meier Estimates of the Probability of Persistent HPV Infection at Subsequent Examinations among Women with Detectable HPV at the Initial Examination, According to HIV Status and According to the CD4+ Count among HIV-Seropositive Women.

more per cubic millimeter to have positive HPV tests during subsequent examinations (P<0.001).

Persistence of HPV Infection

Persistent infection with a high-risk type of HPV may be necessary for the development of high-grade squamous intraepithelial lesions and invasive cervical cancer. We defined persistent infection as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months. HIV-seropositive women were more likely to have persistent HPV infections than HIV-seronegative women (24 percent vs. 4 percent, P<0.001) (Table 1). Among the seropositive women, 19 percent with CD4+ counts of 500 or more per cubic millimeter, 24 percent with counts of 200 to 499 per cubic millimeter, and 33 percent with counts of less than 200 per cubic millimeter had persistent HPV infections (P=0.23) (Table 2).

Fourteen percent of the HIV-seropositive women and 3 percent of the HIV-seronegative women had persistent infections with HPV-16–associated viral types (P=0.004) (Table 1). Persistent infections with HPV-18–associated viral types were found in 8 percent of the HIV-seropositive women but in none of the HIV-seronegative women. Overall, infections with high-risk HPV types (those associated with HPV-16 or HPV-18) were persistent in 20 percent of the seropositive women and 3 percent of the seronegative women (P<0.001). The proportions of women who had persistent infections with other HPV types were also higher in the seropositive group than in the seronegative group. However, the distribution of HPV types was similar in the two groups, and HPV-16–associated types were the most common in both. Figure 3 shows the pattern of HPV shedding in the women with persistent HPV-16 infections. Although HPV detection varies from examination to examination, most women with persistent HPV-16 infections shed some type of HPV DNA at almost every examination.

Risk Factors for Persistent HPV Infection

In the univariate analysis, in which we controlled for the number of examinations, factors significantly associated with persistent HPV infection were HIV

Table 1. Persistent HPV Infections among Women without Squamous Intraepithelial Lesions at the Initial Examination, According to HPV Type and HIV Serologic Status.*

HPV Type	HIV-Seropositive Women (N=220)		HIV-Seronegative Women (N=231)	
	persistent HPV infection	ratio of persistent infection to any infection†	persistent HPV infection	ratio of persistent infection to any infection†
	%	no. persistent/no. any (%)	%	no. persistent/no. any (%)
High risk				
HPV-16–associated (16, 31, 33, 35, or 58)	14.1	31/86 (36.0)	3.0	7/38 (18.4)
HPV-18–associated (18 or 45)	8.2	18/47 (38.3)	0	0/13
Intermediate risk (51 or 53)	6.4	14/36 (38.9)	0.9	2/16 (12.5)
Low risk (6, 11, 43, or 44)	1.8	4/25 (16.0)	0.4	1/12 (8.3)
Any of the above	24.1	53/123 (43.1)	3.9	9/58 (15.5)
Novel	8.6	19/80 (23.8)	3.9	9/45 (20.0)

*A persistent infection was defined as the detection of the same type of HPV at two or more consecutive examinations during a period of 3 to 12 months.

†The ratio was calculated as the number of women with the specific type of HPV detected at two or more examinations during a period of 3 to 12 months divided by the number of women in whom the HPV type was ever detected.

seropositivity, a CD4+ count of less than 200 cells per cubic millimeter, less than 12 years of education, and a history of injection-drug use (Table 2). Unmarried women were more likely to have persistent HPV infections than married women. In the multivariate analysis, after adjustment for age, race or ethnic group, education, marital status, history of prostitution, history of injection-drug use, condom use, smoking, and history of cervical disease, HIV-seropositive women with CD4+ counts of less than 500 per cubic millimeter and those with counts of 500 or more per cubic millimeter were more likely to have persistent HPV infections than HIV-seronegative women. Being unmarried and having a history of injection-drug use remained significantly associated with persistent infection in the multivariate model with all the above-listed risk factors.

New HPV Infections

Forty-eight of 151 women (32 percent) who had negative HPV tests at the first and second examinations had detectable HPV at a subsequent examination. The rate of new infections among the women with initially negative HPV tests was 11 per 100 examinations in the HIV-seropositive group and 9 per 100 examinations in the HIV-seronegative group. The detection of new HPV infections in women with previously negative HPV tests was not associated with serologic status or with sexual activity since the preceding examination. The detection rate was 9 per 100 examinations among the women who reported no sexual activity since the prior examination, 9 per 100 examinations among those who reported intercourse with consistent use of condoms, and 12 per 100 examinations among those who reported intercourse with intermittent or no use of condoms ($P=0.72$). Among the women who became positive for HPV after two consecutive negative tests, 9 of 21 who were HIV-seropositive (43 percent) and 5 of 27 who were HIV-seronegative (19 percent) reported no sexual activity since the preceding examination.

DISCUSSION

HIV seropositivity and HIV-induced immunosuppression are known to be associated with an increased prevalence of anogenital HPV infections in men and women.[1-7] This association involves HPV infections of all types, as well as infections with multiple types of HPV, including those associated with neoplasia, such as HPV-16 and HPV-18. The increased prevalence of these infections suggests that HIV-seropositive women are at increased risk for squamous intraepithelial lesions and invasive cancer of the cervix, vagina, vulva, anus, and perianal region. HIV-associated alterations in the natural history of HPV infection may also influence the risk of HPV-associated disease in HIV-seropositive women.

TABLE 2. PERSISTENT HPV INFECTIONS AMONG WOMEN WITHOUT SQUAMOUS INTRAEPITHELIAL LESIONS AT THE INITIAL EXAMINATION, ACCORDING TO SOCIODEMOGRAPHIC CHARACTERISTICS AND POTENTIAL RISK FACTORS FOR HPV INFECTION.

VARIABLE	NO. OF WOMEN*	PERSISTENT HPV INFECTION†	ODDS RATIO (95% CI)‡
		%	
HIV status			
Seropositive	220	24.1	7.5 (3.6–16)
Seronegative	231	3.9	1.0
CD4+ count in HIV-seropositive women			
<200/mm³	42	33.3	2.8 (1.1–6.8)
200–499/mm³	74	24.3	1.1 (0.48–2.4)
≥500/mm³	73	19.2	1.0
Age			
<29 yr	98	17.3	1.1 (0.48–2.3)
30–39 yr	230	10.9	0.6 (0.31–1.2)
≥40 yr	122	15.6	1.0
Race or ethnic group			
Non-Hispanic black	197	14.2	1.1 (0.51–2.2)
Hispanic	130	14.6	1.2 (0.52–2.5)
Non-Hispanic white	113	11.5	1.0
Marital status			
Married	147	6.8	0.3 (0.14–0.66)
Unmarried	304	16.8	1.0
Education			
<12 yr	185	15.7	1.5 (0.83–2.7)
≥12 yr	264	12.1	1.0
Smoking status			
Current smoker	299	14.0	1.3 (0.70–2.5)
Nonsmoker	152	13.2	1.0
Use of injection drugs			
Yes	159	18.9	2.7 (1.3–4.3)
No	291	10.7	1.0
History of prostitution			
Yes	91	13.2	0.9 (0.42–1.9)
No	359	13.6	1.0
History of cervical disease			
Yes	34	23.5	1.9 (0.74–3.4)
No	417	12.9	1.0

*For some variables, numbers do not add up to totals because of missing data.

†A persistent infection was defined as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months.

‡Odds ratios and 95 percent confidence intervals were calculated by logistic-regression analysis for each variable separately, with adjustment for the number of examinations as an indicator variable. CI denotes confidence interval.

In women in the general population, the shedding of HPV from the lower genital tract is highly variable, and several studies have shown that persistent shedding of high-risk types of HPV is an important factor in the development of squamous intraepithelial lesions of the cervix.[9] If HIV infection causes persistent HPV shedding, this effect may promote the development of anogenital squamous intraepithelial lesions and cancers in HIV-seropositive women.

In our study, we found that HPV shedding was highly variable in both HIV-seropositive and HIV-seronegative women. Of the women examined three or more times, only 49 percent in the HIV-seropos-

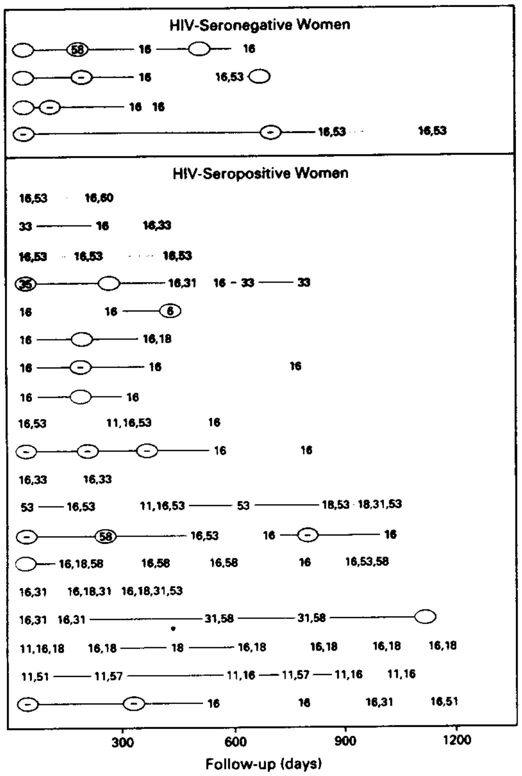

Figure 3. Patterns of HPV Detection in Women with Persistent HPV-16 Infections.

Four HIV-seronegative and 19 HIV-seropositive women had persistent infections with HPV-16. Each woman is represented by a horizontal line, and each examination by a colored circle or oval. Green circles represent the detection of HPV-16; blue circles the detection of an HPV type other than HPV-16 that was identified at least twice in the same patient; yellow circles the detection of HPV that could not be typed or was a type detected only once in the patient; and gray circles undetectable HPV.

itive group and 42 percent in the HIV-seronegative group were consistently positive or negative for HPV at all examinations. In many women, several different HPV types were detected at different examinations. Therefore, studies that have tested HIV-seropositive women for HPV infections on a single occasion may have considerably underestimated the prevalence of such infections. In our study, the cumulative prevalence of infection with any type of HPV after four examinations (during approximately two years of follow-up) was 95 percent in the HIV-seropositive women with CD4+ counts of less than

500 per cubic millimeter and 74 percent in those with CD4+ counts of 500 or more per cubic millimeter. After four examinations, the cumulative prevalences of infection with HPV-16 and HPV-18, high-risk "oncogenic" types of HPV, were 21 percent and 22 percent, respectively, in HIV-seropositive women. These cumulative prevalences, which are considerably higher than the point prevalences in our previous study,[7] indicate that most HIV-seropositive women have cervicovaginal HPV infections and that a large proportion of these women are infected with high-risk types of HPV.

Few studies have determined the cumulative prevalence of anogenital HPV infections in women in the general population. In a study of predominantly white middle-class women with normal cervical cytologic findings, 26 percent had HPV in cervicovaginal-lavage specimens, detected with a PCR assay, at the first visit.[17] After two visits, the cumulative prevalence was 36 percent.[17] Similarly, in a population-based study of 276 young women in Sweden, HPV DNA was detected in 21 percent of the women at the initial visit, and the cumulative prevalence was 25 percent after two examinations, with the use of a nested-PCR method to amplify HPV DNA from cervical scrapings.[18]

Persistent infection with high-risk types of HPV appears to have a central role in the development of squamous intraepithelial lesions and invasive cervical cancer. In a cohort of women with abnormal cervical cytologic findings, Ho et al. found that persistent infection with specific types of HPV resulted in chronic cervical dysplasia.[19] However, little is known about the persistence of HPV infection, or about the relation between persistent infection and the development of squamous intraepithelial lesions, in HIV-seropositive women. In our study, both HIV seropositivity and higher levels of immunosuppression were important determinants of persistent HPV infection. HIV-seropositive women were about seven times as likely to have persistent infection as HIV-seronegative women, and women with CD4+ counts of less than 200 per cubic millimeter were more than twice as likely to have persistent infection as those with counts of 500 or more per cubic millimeter. The higher frequency of persistent HPV infection in HIV-seropositive women than in HIV-seronegative women may explain why squamous intraepithelial lesions occur so frequently in HIV-seropositive women.

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